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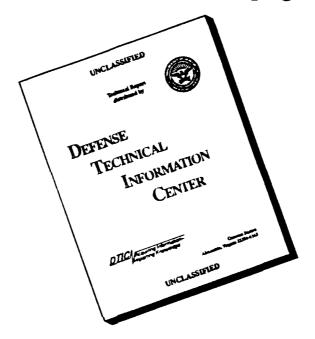
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13. ABSTRACT (Maximum 200 words)

The Human BrainMap Database is a software environment for meta-analysis of human functional brain mapping experiments. In brief, BrainMap relates brain locations with behavioral functions. For any brain region, the behavioral conditions associated with that region can be returned. Conversely, for any behavioral function, the brain regions supporting that behavior can be retrieved.

BrainMap is composed of three main parts: a relational database, graphical user interface (GUI), and a data-entry interface. BrainMap's database is constructed in a natural hierarchy. The highest level is the paper. Each paper is divided into one or more experiments. An experiment is a grouping (typically a pairing) of behavioral conditions for which differentially activated locations are reported. Behavioral conditions are specified for each experiment. Methodological details are specified for each experiment, including imaging modality, tracer, patient population, etc. Each experiment reports one or more activated locations, the lowest level of the hierarchy. Each location (i.e., each x-y-z coordinate) carries its links up the hierarchy, allowing information at the experiment and paper levels to be rapidly retrieved.

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Proceedings of
Workshop I,
The Human BrainMap Database

San Antonio, Texas
November 29, - December 1, 1992

Peter T. Fox, M.D. and Jack L. Lancaster, Ph.D.
January, 1993

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The following is a report on the first workshop of the Human BrainMap Database. The Human BrainMap Database: Workshop I took place in San Antonio, Texas from November 29 through December 1, 1992. Workshop I was the first meeting of the BrainMap Advisory Group. The purpose of Workshop I was to provide the Advisory Group with a detailed description of the Human BrainMap Database and to receive, in return, their critique of the BrainMap concept and its current implementation.

I.   THE BRAINMAP CONCEPT. The Human BrainMap Database is a software environment for meta-analysis of human functional brain mapping experiments. In brief, BrainMap relates brain locations with behavioral functions. For any brain region, the behavioral conditions associated with that region can be returned. Conversely, for any behavioral function, the brain regions supporting that behavior can be retrieved.

BrainMap is composed of three main parts: a relational database, graphical user interface (GUI), and a data-entry interface. BrainMap's database is constructed in a natural hierarchy. The highest level is the **paper**. Each paper is divided into one or more **experiments**. An experiment is a grouping (typically a pairing) of behavioral conditions for which differentially activated locations are reported. **Behavioral conditions** are specified for each experiment. Methodological details are specified for each experiment, including imaging modality, tracer, patient population, etc. Each experiment reports one or more activated **locations**, the lowest level of the hierarchy. Each location (i.e., each x-y-z coordinate) carries its links up the hierarchy, allowing information at the experiment and paper levels to be rapidly retrieved.

BrainMap's GUI is the means through which a user interacts with the database. The GUI contains a digital atlas of the human brain adapted from the atlas of Talairach et al. (1967). Anatomically driven searches can be initiated by simply "paging" through the atlas and "clicking" on the area of interest. Anatomical searches can also be initiated by selecting an area by name (e.g., anterior cingulate gyrus). Searching initiated by behavioral data is driven by text fields, also using a "point-and-click" interface. Three discrete axes are used for describing behavioral experiments.

The Entry Interface was designed for in-house use at the Research Imaging Center in maintaining the common version of the BrainMap database. Its structure reflects that of the Database.

A few pertinent negatives may help to avoid preconceptions. BrainMap is not an archive of raw image data; it contains reduced data ("cooked" data), ready for meta-analysis. BrainMap is not a "laboratory organizer," like the BrainBrowser™ (Bloom, 1991); it performs meta-analysis of an entire literature. BrainMap is not a teaching tool for neuroanatomy; it is a tool for use by the functional brain-mapping research community. BrainMap is not a tool for post-processing or analysis of raw data, like statistical parametric mapping (Friston et al., 1989) or change-distribution analysis (Fox et al., 1988). The laboratory of origin reduces the data into a format amenable to meta-analysis before entry into BrainMap. BrainMap is not an electronic bulletin board, like the Worm Community System (Schatz, 1991) nor a citation index, like MedLine; BrainMap is an environment for in-depth exploration and interactive meta-analysis of the experimental literature of an expanding field.

II.   CURRENT STATUS OF THE HUMAN BRAINMAP DATABASE. BrainMap was developed by Peter T. Fox and Jack L. Lancaster at the Research Imaging Center of the University of Texas Health Science Center at San Antonio. As the BrainMap software matured,

the developers recruited an Advisory Group to provide external critique of the concept, its implementation, and overall organization of the BrainMap project. The Advisory Group are highly respected members of the neuroscience community, with emphasis on human brain mapping, cognitive psychology, and imaging science. The laboratories of the Advisory Group are the beta-test sites for the BrainMap software. Workshop I was the first meeting of the Advisory Group.

Initial developmental funding has come from the MacDonnell Foundation, IBM, and the Office of Naval Research. Current developmental funding is provided by the Low-Beer Foundation. Workshop funding came from several sources (see below, VIII. Workshop Budget and Funding). Written reviews of the BrainMap project were provided by the NSF (in response to a proposal for ongoing support) and by the NIMH (in response to the Workshop I funding proposal). The NSF proposal is being resubmitted, seeking ongoing support of software development. A second NIMH proposal is being submitted, seeking funding for Workshop II.

III.   WORKSHOP GOALS. Workshop I was the first formal presentation of the BrainMap concept and the BrainMap software to the Advisory Group. In addition to the Advisory Group, international observers with expertise complementary to this enterprise were invited to attend. To advise in the development of this tool, an Advisory Group was formed. The purpose of Workshop I was to receive a critique of concept and to advise on further software development and organization issues.

The Specific Goals of Workshop I were:

1.   Assemble and Organize the Advisory Group
2.   Introduce Concept, Developers to the Advisory Group
3.   Explicate and Demonstrate BrainMap Software to the Advisory Group
4.   Allow "Hands-on" Trials
5.   Initial Critique of: Concept, Design, Implementation
6.   Address Criticisms Provided by Grant Reviewers (NSF, NIMH)
7.   Prioritize Additions and Modifications to software and data sets
8.   Discuss/Suggest Funding Mechanisms
9.   Assess Desired Scope
10.   Distribute Software and Launch Beta Testing

IV.   WORKSHOP ATTENDANCE. All attenders were scientists from human neurophysiological imaging (including PET, MRI, MEG, EEG), human neuroanatomy, primate neurophysiology and neuroanatomy, neuropsychology and cognitive psychology, imaging physics, and computer science. Forty-one scientists represented 33 institutions of higher learning in ten countries: Australia, Canada, England, France, Germany, Hungary, Japan, Russia, Sweden, and the United States. The intramural research programs of the National Institute of Aging, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the Los Alamos National Laboratory were represented. Program officers from the National Science Foundation, the Office of Naval Research, and the Low-Beer Foundation attended. A list of attenders and their affiliations is appended.

V.   WORKSHOP ORGANIZATION. The Workshop consisted of five half-day sessions.   In Session I, workshop participants were brought "up-to-speed" on the BrainMap project with

descriptions of the concept, the project's history, and development to date. Session II was a hand-on session, in which all participants "test-drove" the BrainMap software. In Session III, two models of scientific community databases were presented. Session IV was a critique of concept in the form of open discussion. Session V was a summing up. Formal presentations were limited to Sessions I and III.

SESSION I: Project Background, History, and Current Status. Moderator: Jack L. Lancaster. This session was composed of formal informational presentations about the BrainMap project and the functional characteristics of the BrainMap software. The speakers and presentation titles were:

>Peter Fox. *History, Goals and Current Status of The Human BrainMap Database Project.*

>Jack Lancaster. *Design Plan for the BrainMap Software.*

>Wendy Davis. *Data Entry and Distribution.*

>Shawn Mikiten. *Using BrainMap.*

SESSION II: "Hands On" Introduction to BrainMap. Moderators: Peter Fox and Jack Lancaster. This session took place at the Research Imaging Center. Ten computers operating the BrainMap Database were available. All participants were taught how to use BrainMap and allowed to conduct searches and create cross-study comparative plots. BrainMap developers were on hand to receive comments and suggestions.

SESSION III: Toward a Philosophy of Databasing and Data Sharing in the Human BrainMapping Community. Moderator: Chris Wood. This session laid a groundwork for the open discussion that took place in Sessions IV and V. Two invited speakers made formal presentations of existing databases. A panel discussion with participants chosen for their experience in PET imaging, databasing, and datasharing brought many additional issues to light.

The CHILDES Database. Brian MacWhinney.

>MacWhinney described the Child Language Development System (CHILDES), a database of linguistics and cognitive science. The CHILDES project was started in the early 1980s and has been continuously funded and well used. MacWhinney's experiences and observations were extremely relevant for the BrainMap project. MacWhinney commended the BrainMap effort both conceptually and organizationally.

The Worm Community System: A Model for electronic datasharing in the biological sciences. Bruce Schatz.

>Schatz described the Worm Community System, a system developed for molecular biologists mapping the genome of the C. elegans (worm). This system is UNIX/X-windows/MOTIF based. It features many very elegant tools, including an electronic bulletin board, electronic publishing, and rapid cross-referenced access to the "Worm" literature. The Worm Community System clearly sets a standard for using a highly sophisticated user interface and a tool for rapid interactions in a scientific community.

Schatz was particularly impressed with the progress already made by the functional brain mapping community in achieving standards for data processing and reporting (see Discussion Issues 2 and 3 and Appendix I.)

Data Sharing in the Human Brain Mapping Community: Philosophical and Sociological Issues. Panel Members: Alan Evans, Peter Fox, Jon Heather, Brian MacWhinney, John Mazziotta, Steven Petersen, Bruce Schatz, Robert Thatcher, Leslie Ungerleider.

SESSION IV: Critique of Concept and Problem Solving. Moderator: Alan Evans.

The bulk of the open discussion took place in this session. Dr. Evans directed the discussion through a wide range of issues, summarized below (DISCUSSION ISSUES).

SESSION V: Summary and Plan of Action. Moderator: Peter Fox.

In this session, the discussion of the previous session was recapitulated for the sake of establishing consensus and priorities. These priorities are refelected in the summary of our discussions (below, VI. Discussion Issues).

Working Committees (Interest Groups) were formed. These were: 1) Behavioral Categorization, 2) Anatomical Nomenclatures, 3) Antatomical Spaces and Standards, 4) Statistical Descriptors & Standards, 5) EEG/MEG Inclusion, and 6) Interfaces to Other Applications. A full listing of Committee chairpersons and membership is appended (Appendix E).

Software was distributed to all Advisory Group members and to several additional participants who expressed strong interest. The software distribution included: 1) The BrainMap Graphical User Interface (a SuperCard™ standalone application), 2) the digital atlas (as a library of pict files), 3) the Data-Entry Interface (a SuperCard™ standalone application), and 4) a client version of Oracle™ (licensed through the imaging center). A full listing of beta-test sites is appended (Appendix D).

VI.   DISCUSSION ISSUES. Discussion items arose from concerns of the development team, comments from BrainMap grant reviewers (NSF, NIMH), and participants' comments. Sessions IV and V were devoted to open discussion.

1.   Critique of Concept. The utility and overall desirability of BrainMap received strong endorsement but only brief discussion. Acceptance of this tool was virtually immediate, although none of the attendees had previously received more than a brief description of this project. The consensus was that -- after numerous "neuroscience database workshops" in which a great variety of database projects were considered without tangible results -- it was refreshing to have a specific project on the table, and both startling and energizing that so much had already been accomplished. The strength of the Workshop's endorsement of BrainMap was best reflected in the enthusiasm with which participants suggested additions and encouraged the development of mechanisms to continue active participation in the development process (e.g., an electronic bulletin board).

After use of the BrainMap software, participants agreed that this tool would be useful in several ways. Rapid review and explicit comparison of large amounts of data would promote deeper insights and facilitate hypothesis generation. Making discodances among studies explicit, it would

facilitate the design of new experiments to resolve ambiguities. Bringing together unprecedented number of studies, it can even serve to test new hypotheses directly from existing data.

2. Human Brain Mapping as a Model Community for a Neuroscience Database. BrainMap relates human behaviors to brain locations. In the broad scope of neuroscience, this is a very small piece. It is, however, a very important and "databaseable" piece. The reason for this is that the PET community has achieved good conformance to a standard method of describing brain locations, and of performing image processing and statistical analysis. These methods allow studies to be summarized in a very dense format that is very amenable to database storage and retrieval. Further, human brain mapping is an area of interest to a very wide scientific and clinical community.

Although many participants, whose areas of research lay outside the current scope of BrainMap, expressed the desire that BrainMap should be expanded to include their research area, no one faulted the initial choice. Rather, they understood the need for this choice and strongly encouraged the development of algorithms for allowing other types of data to be reported in bicommissural coordinates. As these tools are developed, BrainMap will be extended to include functional MRI, EEG, MEG, and lesion-deficit observations. Van Essen, Rakic, and Carmen strongly urged the development of mechanisms that would allow primate single-unit physiology to be included, as these observations have served as the basis for PET experiments and vice versa. Clearly, there will be many additions to and spinoffs from BrainMap as a model for database development in the neurosciences.

3. Relation to the Human Brain Project. The Human Brain Project of the NIMH has set the goal of creating a neuroscience database capable of *integrating knowledge across species* and at all levels of study, ranging from molecular biology and membrane physiology, at one extreme, to systems physiology and cognitive science, at the other. Such a grand scheme can only be achieved by starting small and building a piece at a time. BrainMap is intended to be a first small piece in this great puzzle. BrainMap has chosen to start in a well-established area and focus on a database structure that incorporates those data which have been or can be standardized. BrainMap has been featured in several of the workshop's organized by the Human Brain Project, including the meeting at the Society for Neuroscience, 1992. As the Human Brain Project is not yet funded, BrainMap has not yet received support from this project, per se. BrainMap did receive support for Workshop I from NIMH, the prime mover of the Human Brain Project. As the Human Brain Project is launched, BrainMap will seek funding from this source.

4. Stereotactic Coordinates. Bicommissural coordinates are integral both to BrainMap's anatomical retrieval functions and to its data-visualization tools. The inherent limitations of volume coordinates have been exhaustively discussed and are well known. Despite their acknowledged limitations, a viable alternative has yet to be developed. The appropriateness of the use of bicommissural coordinates, therefore, was uniformly accepted.

On the other hand, strong interest in the development of alternative anatomical coordinate systems was expressed. Proposed examples of alternatives to volumetric coordinates included: flattening of the cortical surface into a plane, projection of the cortical surface onto a sphere, and "relaxation" of the infoldings of the cortical surface to create a convex surface. These alternative anatomical spaces will need considerable development before they are useful for reporting functional activation data. Community acceptance as a standard reporting format is an additional problem that must be

solved before these alternative nomenclatures could be considered for use in a database.

5.   The Talairach Atlases. The Talairach atlases (Talairach et al., 1967; Talairach & Tournoux, 1988) are used in the BrainMap database. Graphics for data visualization were derived from several sets of anatomical plates in the Talairach (1967). Coordinate transformations for all plates in Talairach (1967) and in Talairach & Tournoux (1988) are included in the BrainMap algorithms.

Many participants argued for including additional brain data sets in BrainMap, in particular, for data visualization. Data sets suggested included: a high-quality, high resolution, finely sliced MRI data set from a normal volunteer; an averaged MRI brain, as developed by Alan Evans; and an ultra-high resolution brain-image set by cryo-macrotome, as developed Arthur Toga. The sizes of these data sets range from large (a few hundred megabytes) to enormous (over a gigabyte). Manipulation of very large data sets is problematic for the current platform (Macintosh) and even for many high-end workstations. At present, the use of such data sets would be effectively restricted to dedicated image-processing workstations (e.g., Silicon Graphics workstations). Few laboratories currently have access to such high-end computers, limiting the utility of such tools.

6.   Choice of Development Environment. Discussions about the choice of development environment were lively. Opinions were as diverse as they were emphatically expressed. No option pleased everyone; no one was shy about arguing strongly for their preferred development environment. Not surprisingly, the same combination of diversity of opinion and individual conviction was seen in the reviewers' comments returned by the NSF before to the conference.

BrainMap is being developed in the *Macintosh operating system (System 7)* using a commercial, graphical-user-interface (GUI) development/prototyping tool (SuperCard™) and a commercial, relational (SQL) database management system (DBMS) (Oracle™). The Macintosh environment was selected for the combination of wide availability, low cost, good graphics capabilities, excellent GUI development tools (i.e., SuperCard™), and the availability of an SQL DBMS (Oracle™). Oracle™, like most commercial DBM systems, runs on a wide range of computer environments and requires very little recoding to move a fully developed database across platforms. SuperCard™ is an interpretive (script-based) window-management system that runs solely in the Macintosh operating system. SuperCard allows very rapid prototyping of fairly sophisticated GUIs. SuperCard™ runs slowly, because it is interpretive rather than compiled, but allows functions written in compiled code to be appended. Oracle™ fully supports the use of SuperCard™. This development environment was chosen after extensive discussions with computer scientists with experience in GUI and database development, including the manager of the Human Genome Database (which also uses an SQL DBMS).

The choice of development environment (Macintosh™/Oracle™/Supercard™) and the decision to port to other environments after prototyping was more advanced had many strong proponents, both among workshop participants and among reviewers of the BrainMap grant proposals. Tools that may both speed development and facilitate later porting (e.g., Faceware) were brought to the attention of the developers. Two alternative development environments were lobbied for most strongly: UNIX/X-windows™/MOTIF™/C with no allowance of special-purpose hardware or proprietary libraries, and UNIX/X-windows™/MOTIF™/C with full use of the of special-purpose hardware or proprietary libraries included in high-end graphical workstations (i.e., Silicon Graphics™). The use of a "generic" UNIX environment would clearly speed up the operation of

the database, but significantly slow the process of development. Development on a dedicated graphics workstation would allow "real-time" manipulation of very high quality, 3-D, brain images and brain models but would severely limit the potential user community. The lack of consensus was clear evidence that there is no "right answer." No overwhelming reasons to change the choice of development environment were presented.

Porting from a prototyping environment to a mature environment is planned in three stages. The first stage of the port will move the DBMS to a UNIX platform, accessed by the Macintosh/SuperCard interface over a network. This is expected to be accomplished rapidly. The second stage of the port will be to build a a high-speed version of BrainMap on the Macintosh. This will be accomplished by replacing SuperCard interpretive code with compiled "C" code, with interface development in "Faceware". This will take some time and will not be attempted until the SuperCard prototype GUI stabilizes. The final stage will be to port the high-speed version to a UNIX platform (probably a SUN workstation) as an X-windows/MOTIF application.

7.   Distributed Development. Both NSF and NIMH reviewers of the Workshop I proposal raised the possibility of distributed software development, likening the BrainMap project to a software "users group." This comparison is inaccurate. Distributed development (in the sense of open distribution of source code for off-site modification) is appropriate for modular applications, for example, where functions are added as modules to a display environment or where software libraries are shared and incorporated into independent applications. BrainMap is not a collection of applications or a library of development tools that can be readily shared for distributed development. BrainMap is an integrated software tool, containing a rather complex database, requiring standardized data coding and entry. Integration and integrity checks are needed throughout the database and between database and the two *interfaces* (user interface and entry interface). Allowing sites to make *ad hoc* alterations to BrainMap would serve only to create a myriad of incompatible versions and would create a very significant risk of undermining the entire project. Both database models discussed at the Workshop (CHILDES and the Worm System) were centrally developed and subsequently distributed. MacWhinney strongly endorsed the model adopted by BrainMap of central development and an Advisory Group for beta testing. Distributed development, in the sense of open distribution of source code, was vetoed. On the other hand, two vehicles for shared development were proposed and enacted: Working Committees, and Co-Development Projects.

Working Committees were created to continue discussion of unresolved issues (see Appendix E). One function of the Working Committees is to provide more formal criticism and suggestions for refinement of specific aspects of BrainMap to be implemented by the BrainMap development team. Working Committees may also address problems that will require more substantial development efforts; for example, new tools for data display or statistical analysis. These projects may be undertaken by the BrainMap development team alone or may require Co-Development Projects. For example, the MEG/EEG working committee will address strategies for incorporating EEG data into BrainMap. A first draft of the information fields needed to describe EEG behavioral paradigms, and its temporal data structures will require additions to both the database and the interface and will be performed by the BrainMap team. A method for computing bicommissural coordinates for EEG data will probably require a co-development effort.

Co-Development Projects will consist of collaborations between the BrainMap development team and persons wishing to create additional functions to be incorporated into BrainMap. Several Co-

Development Projects are being discussed. Donald Tucker (University of Oregon) has proposed a technique for computing bicommissural coordinates for EEG that he would like to co-develop with the BrainMap development team. The inclusion of alternative image sets for data visualization (e.g., the averaged MRI developed by Alan Evans), will be best accomplished as a Co-Development Project.

8.   Internet Distribution/Contribution. Virtually all participants have access to Internet. Three uses of Internet were discussed/recommended. First, distribution of new software versions and data updates will be via FTP over Internet. Second, development of an electronic bulletin board for BrainMap was recommended and will also be explored. Third, serving the database component (SQL/Oracle™) of BrainMap over Internet from a central UNIX host computer to a local Macintosh running the GUI may be a very cost-efficient means of increasing the operating speed, simplifying distribution, and reducing the need for local disc space. Testing this strategy will be a high priority. It is recognized that serving images over the Internet is quite slow. At present, graphics are locally stored (i.e., with the GUI), rather than in the DBMS.

9.   Local Data Entry. A very high level of enthusiasm was expressed for local data entry, for two reasons. First, participants wanted the option of adding their own data, both published and unpublished, to their local version of the database. This neither assumed nor denied a willingness to contribute "raw" data (see below, 11. Unpublished Data). Second, participants expressed a willingness to code their data for entry in the central version.

Data is entered into BrainMap through the entry interface. The entry interface was not intended for external distribution. Nevertheless, in view of the strong interest in local data entry, the entry interface was distributed. Local coding of data (i.e., by the primary investigator) will greatly speed the growth of the BrainMap database and do much to assure accurate interpretation and proper coding of the data.

10.   Data Quality / Review Mechanisms. The widespread acceptance of bicommissural coordinates and voxel-based analytic methods by the PET functional activiation community greatly simplifies the problem of data review and data quality. Virtually all PET laboratories active in brain mapping are publishing activation-location coordinates and statistical significance levels in very comparable formats. Noncoordinate anatomical descriptions are poorly standardized. Methods for describing behavioral conditions are not standardized.

At present, only papers that report activation locations using bicommissural coordinates are being included in BrainMap. This includeds PET and functional MRI. No MEG or EEG studies are yet available (see 3, above). Paper review and data entry are performed by a review group of clinical neuroscientists (neurologists, psychiatists, and clinical neuropsychologists). Papers are reviewed and coded by one reviewer; the entire entry then checked by at least one other reviewer. Both reviewers make notes of questions or problems in paper entry. Activation-location coordinates are entered exactly as published. (The database contains parameters to correct for differences among atlases.) Alternative anatomical descriptions (e.g., Brodman's area, gyral name, etc.) require some interpretation by the reviewer. Behavioral categorization is also coded by the reviewer, following a predefined scheme.

Several investigators expressed enthusiasm for author entry of papers, with review by the BrainMap review group before entry into BrainMap. This can best be accomplished by

distributing the Entry Interface in a version that creates files to be transmitted via Internet or diskette. With authors coding their own studies, the entry process will be greatly speeded. A goal for the upcoming year (i.e., before Workshop II) is to include the entire literature of data published in the bicommissural coordinate space.

Entry of unpublished data (below, Item 11) will raise several problems, not the least of which will be quality assurance. The current policy of entering only published data assures that all work has been subject to peer review. More elaborate review mechanisms will need to be implemented for inclusion of unpublished data. This will be an item of discussion for Workshop II.

11. "Private" Data. Data that has been reduced for publication in accordance with the current post-processing formats, but is not explicitly available in a published pape,r falls into three categories: deeper-than-published data, pre-published data, and unpublished data.

Deeper-than-published data amplifies a published manuscript. A very powerful form of data amplification is inclusion of activation locations below the threshold for statistical significance reported in a published work. Consider, for example, a paper published reporting ten locations at a significance level of $p < 0.001$. Although the paper reported only these 10 sites, BrainMap could include additional activation sites to an arbitrarily large "p" value. Filtering a search by significance level, activation trends could be explored when developing hypotheses and designing experiments. Persuading authors to contribute these additional locations and significance values will be more difficult than the design changes needed to accomomdate them. Amplification and standardization of the description of behaviors and methods also has an obvious benefit.

Prepublished data can be either accepted (in press), submitted (in review), or unsubmitted (incomplete). In-press data poses no logistical problems and would be a very valuable addition. Once BrainMap is distributed by Internet, data could be available almost immediately following journal acceptance. For some journals, BrainMap availability could precede actual publication by a year or more. As brain mapping is a rapidly evolving field, including in-press data would be extremely beneficial in preventing unwitting duplication of effort.

Pilot studies and negative studies that are not intended for publication would also be quite valuable. Many studies are published only after a pilot experiment is redesigned and repeated. The difference between the pilot experiment and the final experiment can be quite informative for meta-analysis. Negative studies could help those designing experiments to avoid repeating the mistakes of their colleagures.

The logistics of including unpublished data vary with the type of data. Amplification of published data and inclusion of in-press data is logistically simple. Inclusion of data not yet peer-reviewed would create a need for a more formal review mechanism to assure data quality.

12. Raw Data. "Raw" data -- data less reduced than published data -- poses tremendous logistical problems for a common database such as BrainMap. The most obvious problem of unreduced data is size. Tomographic raw data can be huge. For PET and MRI, a single, two-dimensional slice contains tens-of-thousands of pixels (100 x 100; 256 x 256; 512 x 512). Each pixel has 8, 16, or 24 bits. A typical scan is a three-dimensional matrix, containing between 10 and 50 slices. In a behavioral, activation study, each subject has at least 2 scans (task and control) and as many as ten or twelve scans. Each experiment reports on a minimum of 3 or 4 subjects and

often 10 or even 20 subjects. Published papers may report a single experiment, but more often report a series of converging experiments. Thus, the raw data is quite massive.

The problem is actually larger than it appears at first look. As the data is progressively reduced, intermediate forms of data are created. Should each of these intermediate forms of data be stored and available? The sequence of steps used in each laboratory differ, making the intermediate data forms different among laboratories. How are we to keep track of all of these different data forms?

"Raw" data is only useful if it can be analyzed. Providing raw data implies that each database user has all of the software needed to analyze the raw data "from scratch." Analytic software is not easily acquired. Many laboratories have built analytic tools that are idiosyncratic to their hardware and software environment, making "porting" this software to other systems quite time-consuming. Analytic packages are often built with using commercial image-processing libraries (e.g., MatLab™ or IDL™). Rights to use these libraries can cost tens of thousands of dollars, with similarly high yearly renewal costs. Some laboratories have commercialized their software, with individual packages costing several thousands of dollars. Laboratories actively engaged in functional mapping will have software on hand, capable of processing their own data; but it may well not be able to handle similar data from other laboratories. It will certainly not be able to accommodate data from every modality that will be included in BrainMap. PET analytic software is incapable of handling raw EEG or MEG data.

BrainMap is possible because brain-mapping laboratories reduce their data to a common format that is independent of the modality of origin, the laboratory of origin, or the exact nature and sequence of the intermediate processing steps. Although the ideal of archiving raw data is superficially appealing -- data uncorrupted by any processing could be available for new forms of analysis as they arise -- providing useful access to raw data is a logistical nightmare. Even geneticists do not archive raw data in their public databases.

13. The Sociology of Sharing. Having emphasized the logistical impediments to data sharing, the sociology of science poses far greater hurdles. The ability to deeper-than-published, prepublished, and unpublished data is very appealing. Workshop participants were very anxious to have the BrainMap Entry Interface to create local (in-house) versions of BrainMap with these various types of private data. Yet, discussions became heated whenenver the prospect was raised of making these in-house data available in a common version. Data are a hard-won treasure. They provide the leverage to win grants and advance careers. Making data generally available reduces an investigatior's competetive edge. Where is the motivation to help the community, when the recipients use this assistance to compete with the contributor? Should investigators be "required" to submit data for the common good? If so, through what mechanism? Journals in the gene-mapping field require database submission before review by a journal. How did this occur, and how is it viewed by the community? The model established by the geneome mapping community needs to be studied very carefully to see whether and how its lessons can be applied to the brain mapping community. Data sharing in the brain mapping community is just beginning. It will need to approached carefully and gradually to prevent a backlash of paranoia.

14. Methodological Standards. To define the initial scope of the project and have some well-defined data to enter, only data reported in bicommissural coordinates is being entered into BrainMap. Similarly, fields describing statiscal significance were designed with voxel-based statistical methods in mind. Thus, certain methodological standards are implicit to the the design of

BrainMap.

The discussion focused on whether further methodological standards (e.g., behavioral activation methods) should be formally developed and promulgated. The consensus of opinion was that this should be avoided so far as is possible. If laboratories differ in methodology, these differences should be reflected in fields in the database. The limiting factor is whether the methodological differences make comparisons among studies illogical or nonsensical.

A full description of methods implies a rather comprehensive set of fields in the database for describing the many permutations of behavioral studies. A major goal of the Behavior Committee and the Statistical Committee is to provide recommendations on the fields to be included in describing studies.

15. Database Design. Database design (i.e., the SQL table and relational structures) received very little discussion. This was not unexpected, as the need for additional fields or different search strategies will become apparent only after more extensive use. The SQL structure was substantially reworked in mid-1992, making many improvements over the orginal design. The development team also has quite a number of planned refinements that will be incorporated into the next release.

16. Graphical-User-Interface Design. Many suggestions were made for improving the graphical user interface (GUI). Some were practical; others were more visionary.

A request both practical and emphatically voiced regarded the level of control provided in plotting the results of a search onto the brain-structure diagrams. In the version available for the workshop, all experiments included in any paper retrieved were plotted simultaneously. Participants felt strongly that control of data plotting must extend to individual experiment.

Another desired GUI improvement -- actually a family of improvements -- was to add additional brain images, brain models, and tools to manipulate them for alternative modes of data visualization. For example, several participants wished for a high-resolution set of 3-D MR images that could be rotated about any axis and sliced through any plane as a backdrop for plotting functional activation results. Other suggestions for atlas plates included digitizing the Yakolev collection and making a new set of stained histological sections. Many participants suggested that brain locations have pop up labels to guide those unfamiliar with neuroanatomy. The ability to draw irregular regions in three dimensions and to have searches confined to the bounded regions was suggested. Suggestions were noted and prioritized. We expect that many additional suggestions will be made through the Beta-testing period.

17. Data-Entry Interface. The entry interface was not intended for external distribution. Nevertheless, in view of the strong interest in local data entry, the entry interface was distributed. The entry interface will need to be modified in two major ways. First, local data additions will need to be protected from being overwritten when the local copy of the common version of BrainMap is updated. Second, data coded locally for entry into the common version will need to be stored as a file than can be checked centrally (i.e., at the Research Imaging Center) before incorporation into the common version of E   nMap.

18. Tools for Meta-Analysis. The development of additional tools for formal meta-

analysis and for the development and testing of systems-level models was raised both by the developers and by reviewers of the grant proposal. Participants' responses to these issues were few. When specifically probed on this issue, the responses were that ideas for tools will be prompted by use; initially statistical meta-analysis could be performed with commercially available statistical packages; and only after methods for meta-analysis were developed and tested with such external tools should they be considered for incorporation into BrainMap.

19. New Versions/Beta-Test Mechanisms. Workshop I provided sufficient input for the development of a new version of BrainMap (Version 2.0) Version 2.0 will be distributed at the close of the first quarter. At that time, bug-report forms will be circulated. Submission of bug reports will be by fax. Subsequent releases are planned quarterly.

20. Workshop Size and Composition: *Workshop I.* The purpose of Workshop I was to critique the BrainMap project and promote its development. This goal determined the size, composition,and organization of the workshop. Workshop I was initially planned for 21 participants. This was felt to be the minimum number needed to achieve the stated goals. As funding for the workshop was secured, size was enlarged to a total of 41.

Invitations to participate in Workshop I were carefully weighed. The PET functional activation community was the best represented, as this literature is serving as the paradigm for BrainMap's development. Despite this focus on PET, the breadth of human brain-mapping was surveyed, with well-respected members of the EEG (event-related potentials), MEG, and functional MRI fields in attendance. Additionally, the fields of primate electrophysiology, neuroscience database development, cognitive psychology, imaging physic,s and computer science were represented. Whenever possible, two scientists were brought from each group: a senior scientist with a biological orientation and a broad perspective, and a junior scientist with strong computer skills. (see Appendix B, Workshop Attendance Roster).

21. Workshop II. The need for a second workshop was strongly endorsed. It was recommended that this take place within one year (December, 1993), rather than in 18 months (May, 1994), as had been initially suggested by the developers.

The size and composition of Workshop II were recommended to be very similar to those of Workshop I. The Advisory Group will remain the core of the workshop. A gradual increase in non-Advisory Group attendance was recommended as a means of increasing awareness of and participation in this project, without having the meeting growing to unmanageable size. Allowing participants to bring junior scientists (e.g., graduate students and post-doctoral students) at their own expense was also suggested. The opinion expressed by the NIMH review, that the meeting was "elitist" and should be opened and advertized, was seconded by no one. The impracticality of this suggestion for a working meeting was abundantly clear.

22. Funding Strategies. While BrainMap has a small base of funding (from the Low-Beer Foundation), realization of the full potential of this project will require a steady source of development funding. Concepts for improvements and additions already sketched out by the development team, and the Advisory Group will take years to be fully transformed into working software. By that time,still more advanced concepts will be developed. Ongoing funding is a necessity.

The experience of the CHILDES project was that the program project proved a very good vehicle for ongoing funding. Core funding support development, distribution, and support of core software. Grants should include both research projects based on the core database and of co-development project for additions to the database of both data and software.

For the near term, funding for Workshop II will be sought through an R-13 submitted to the NIMH. Additional support for software development will be sought though a resubmission to the NSF. The prospect of a program project or other such mechanism will be considered after the program announcement for the Human Brain Project is released.

23. Meeting Proceedings. Workshop I consisted largely of training and brainstorming. Only two formal presentations were allowed. This format does not lend itself to the usual practice of publishing a meeting proceedings in the form of abstracts for each talk. A proceedings summarizing the discussions has been assembled (i.e., this document). This proceedings is being made available to all agencies providing funding for Workshop I, to all participants of Workshop I, and to all interested parties, upon request.

24. Relation to Journals: Copyrights ans Permissions. For the most part, the data contained in BrainMap is not covered by copyright (i.e., data tables). Several fields in BrainMap, however, are covered by copyright and will require permission for inclusion. Article abstracts, figures, and figure legends will require permission to replicate and distribute. As all BrainMap data reference their source, obtaining permission for use in BrainMap should not be difficult. Negotiating standing permission agreements was suggested and will be explored.

25. A Society for Human Brain Mapping. A motion was raised repeatedly that this group consider the formation of a Society of Human Brain Mapping. This idea has been raised in several other contexts. Overall, this suggestion was well received. As this issue was outside the focus of the present Workshop, no action was taken. This will be on the agenda for Workshop II.

VII. OVERALL OUTCOME. Workshop I: Overall Outcome. The overwhelming consensus was that Workshop I was extremely successful. A very strong confirmation was received on the importance of the BrainMap project. Participants expressed this endorsement not only in words, but through their very active participation in the conference, high interest in ongoing use and critique of the BrainMap software, and strong desire for a series of BrainMap workshops. Participants have been asked to commit to writing their overall impression of the BrainMap concept and its implementation and their view of how best to prioritize development efforts. These "testimonials" will be appended to this report and to future grants submissions.

Resolved Issues:

- Need for Neuroscience Databases
- Human functional brain mapping as a good starting point
- Basic goals of BrainMap: database of human functional brain mapping, relate function and locations, promote meta-analysis.
- Bicommissural coordinates as a common language for anatomy
- Basic structure of BrainMap: SQL database, graphical user interface, brain-visualization tools.
- Need to enhance GUI software

- Need to refine Database structure
- Need to include other types of functional mapping data (e.g., EEG, MEG)
- Beta testing and working committees as vehicles to improve BrainMap.
- Need to meet again in one year at Workshop II.

Unresolved Issues:

- Mechanisms for including "Private" data sets.
- Ultimate scope of distribution & "rules" of participation
- Prioritization of refinements requiring software development
  - Porting to other enviroments
  - Tools for meta-analysis
  - Tools for enhanced visualization
  - Tools for exporting search results
- Relation to (inclusion of) other areas of neuroscience
  - Lesion-deficit studies
  - Resting-state PET/EEG/MEG studies
  - Primate mapping studies
  - Anatomical studies
- Relation to (promotion of) new methods in human brain mapping
  - Alternative "anatomical" spaces (e.g., cortical unfolding)
  - EEG/MEG conversion into Bicommissural space
  - Neural systems modeling from brain-mapping data.

Discussion of unresolved will be continued by the Working Committees via the BrainMap Bulletin Board and other mechanisms and will be reopened for the entire Advisory Group at BrainMap Workshop II.

VIII. WORKSHOP BUDGET and FUNDING: Funding for this workshop was provided by: the Low-Beer Foundation, the Office of Naval Research, the National Science Foundation, the National Institute of Mental Health, the Mind-Science Foundation, G.E. Medical Systems, Hammamatsu Photonics Inc., the Texas Research and Technology Foundation, USAA Insurance Company, and Elscint Inc.

The total costs of this workshop were $55,982. Costs can be broken into the following categories: Lodging: $11,076; Airfare: $31,769; Ground transportation: $660; Meals: $4,273; Audiovisual support: $2,457; Secretarial Support $560; Office supplies & FAX: $143; Commercial software (Oracle): $4,946; and Software media (diskettes): $98.

IX. ACKNOWLEDGEMENTS. BrainMap Workshop I was made possible by contributions from the Low-Beer Foundation, the Office of Naval Research, the National Science Foundation, the National Institute of Mental Health, the Texas Research & Technology Foundation, the Mind-Science Foundation, USAA, Elscint Ltd., Hammatsu Photonics, General Electric Medical Systems, and Wiley-Liss Publishers. Administrative support was provided by Mr. Johnny Conner, Mrs. Sally Faulk, Ms. Chris Sosa, Mrs. Barbara Rowe, Ms. Antoinette Hamilton, Mr. Mark Stewart. BrainMap software was implemented by Shawn Mikiten and Wendy Davis. BrainMap data review, coding, and entry was performed by Dr. Steven Brannan, Dr. Charles Gay, Dr. Mario Liotti, Dr. Richard Mahurin, Dr. Helen Mayberg, Dr. Dianne

APPENDIX A

Workshop Program

HUMAN BRAINMAP DATABASE PROJECT
WORKSHOP I

The Hyatt Regency, Riverwalk
November 29-December 2, 1992
San Antonio, Texas

EVENTS SCHEDULE

SUNDAY EVENING, NOVEMBER 29

7:00-9:00 p.m.   **WELCOMING RECEPTION**
                      Hyatt Regency, Garden Terrace

MONDAY MORNING, NOVEMBER 30

7:30-8:30 a.m.   Continental Breakfast
                      Hyatt Regency, Rio Grande Ball Room Foyer

SESSION I

Project Background, History and Current Status

Jack L. Lancaster, Moderator
Hyatt Regency, Rio Grande Ball Room

8:30-8:40   James J. Young, Ph.D., Dean of Medical School UTHSCSA
                 Welcome and Opening Remarks

8:40-9:30   Peter Fox
                 History, Goals and Current Status of The Human
                 BrainMap Database Project

9:30-10:30   Jack Lancaster
                 Design Plan for the BrainMap Software

10:30-10:45   Break

10:45-11:20   Wendy Davis
                 Data Entry and Distribution

11:20-12:00   Shawn Mikiten
                 Using BrainMap

12:00-1:30   Lunch
                 Hyatt Regency, Garden Terrace

MONDAY AFTERNOON, NOVEMBER 30

SESSION II
"Hands On" Introduction to BrainMap

Peter Fox and Jack Lancaster, Moderators

Research Imaging Center
McDermott Clinical Sciences Building,
University of Texas Health Science Center at San Antonio

1:30-2:15   Depart and travel to Research Imaging Center

2:15-6:00   Simultaneous Sessions:

                              BrainMap Teaching
                              Class Room: McDermott Building Foyer
                              Wendy Davis, Shawn Mikiten, Helen Mayberg, Charles
                              Gay, Roderick Mahurin, Steven Brannan, Dianne
                              Solomon

                              Facility Tour and Project Demonstrations
                              Research Imaging Center Staff

4:00-4:20   Break

MONDAY EVENING, NOVEMBER 30

6:00-8:00   **GENERAL RECEPTION**
                            Entrance Foyer, McDermott Clinical Science Building

8:00-8:45   Depart to Hyatt Regency

TUESDAY MORNING, DECEMBER 1

7:30-8:30 a.m.   Continental Breakfast
                    Hyatt Regency, Rio Grande Ball Room Foyer

SESSION III
Toward a Philosophy of Databasing and Data Sharing
in the Human BrainMapping Communitry

Chris Wood, Moderator
Hyatt Regency, Rio Grande Ball Room

8:30-9:15   Brian MacWhinney
                    The CHILDES Project: A model of electronic datasharing
                    in the behavioral sciences.

9:15-10:00   Bruce Schatz
                    The Worm Community: A model of electronic
                    datasharing.

10:00-10:15   Break

10:15-12:00   Discussion: Data Sharing in the Human Brain Mapping
                    Community: Philosophical and Sociological Issues.

                    10:15-11:30   Panel Discussion: Alan Evans, Peter Fox, Jon
                                  Heather, Brian MacWhinney, John Mazziotta,
                                  Steven Petersen, Bruce Schatz, Robert Thatcher,
                                  Leslie Ungerleider.

                    11:30-12:00   Open Discussion

12:00-1:30   Lunch
                    Hyatt Regency, Garden Terrace

TUESDAY AFTERNOON, DECEMBER 1

SESSION IV
Critique of Concept and Problem Solving

Alan Evans, Moderator
Hyatt Regency, Rio Grande Ball Room

1:30-3:00   BrainMap Software, Projected Modifications and Additions

> 1:30-2:00   Peter Fox: Amplification of Anatomical and
>   Behavioral Search Strategies; including more
>   modalities.
>
> 2:00-2:30   Jack Lancaster: Analytic Tools, and other software
>   improvements.
>
> 2:30-3:00   Lee Pasquali: Distribution Alternatives

3:00-3:20   Break

3:20-5:00   Open Discussion: Critique of Concept and Problem Solving

> Project Desirability, Utility and Expected Impact.
>
> Recommendations for Short-Term Improvement:
> Interface Design, Database Design, Distribution Methods,
> Analytic Tools, Modeling Tools.
>
> Recommendations for Long-term Improvements:
> Platform, environment, data types.
>
> Scope of Distribution, short- and long-term.
>
> Interfacing to "proprietary" software systems (e.g., SPM).

TUESDAY EVENING, DECEMBER 1

6:00   **LaVillita Stroll for non-Advisory Group Attendees**

6:30   Advisory Group Departs to The Argyle
            Hyatt Main Entrance

7:00   **Advisory Group Dinner**
            The Argyle

Aiv

WEDNESDAY MORNING, DECEMBER 2

7:30-8:30 a.m.   Continental Breakfast
                    Hyatt Regency, Rio Grande Ball Room Foyer

SESSION V
Summary and Plan of Action

Peter Fox, Moderator

Hyatt Regency, Rio Grande Ball Room

8:30-10:00   Present and Refine the Plan of Action

                    Prioritize Recommended Changes

                    Time Line for Beta Testing

                    Time Table and Mechanisms for:
                         Bug Reports -- Bug Repair
                         Data Submission
                         Software Upgrades
                         Data Updates

                    Workshop II: Projected Dates and Agenda of

                    Form Committees (as needed)

10:00-10:15   Break

10:15-10:30   Distribute Software to Advisory Group Members

10:30-10:45   Peter Fox
                    Closing Remarks

APPENDIX B

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Bruce Rosen, M.D., Ph.D. (Director Clinical NMR, Massachusetts General Hospital-NMR Center, Harvard Medical School)

Bruce R. Schatz, Ph.D. (Community Systems Laboratory, University of Arizona)

Justine Sergent, Ph.D. (Cognitive Neuroscience Laboratory, Montreal Neurological Institute and Hospital, McGill University)

Arthur Toga, Ph.D. (Associate Professor, Department of Neurology, Laboratory of Neuro Imaging, University of California School of Medicine)

David Van Essen, Ph.D. (Edison Professor of Neurobiology, Head, Department of Anatomy and Neurobiology, Washington University School of Medicine)

C.C. Wood, Ph.D. (Group Leader, Biophysics Group, Los Alamos National Laboratory)

APPENDIX D

Beta-Test Site Roster

Beta-Test Sites - Human BrainMap Database

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APPENDIX E

Working Committees

BrainMap Committees/Working Groups:

Behavioral Categorization

Chairman: Leslie Ungerleider
Susan Chipman
Peter Fox
Balázs Gulyás
M-Marsel Mesulam
Steven Petersen
Michael Posner
Per Roland
Justine Sergent

Anatomical Nomenclatures:

Chairman: George Paxinos
Peter Fox
Patricia Goldman-Rakic
Arthur Toga

Anatomical Spaces and Standards:

Chairman: Jack Lancaster
George Carman
Alan Evans
Peter Fox
Chris Wood

Statistical Descriptors & Standards

Chairman: Karl Friston
Peter Fox
Jon Heather
Bernard Mazoyer
Fran Meizin
Keith Worsley

EEG/MEG Inclusion:

Chairman: Robert Thatcher
Peter Fox
Mario Liotti
Jerry Russell
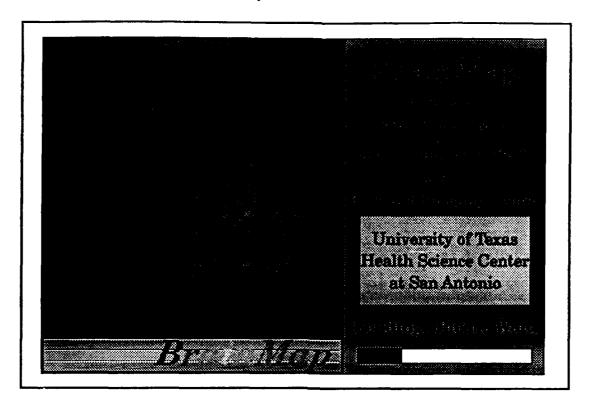Don Tucker
Chris Wood

BrainMap Committees/Working Groups:

Interfaces to Other Applications

Chairman: David Darby
Jack Lancaster
Hugh Lyshkow
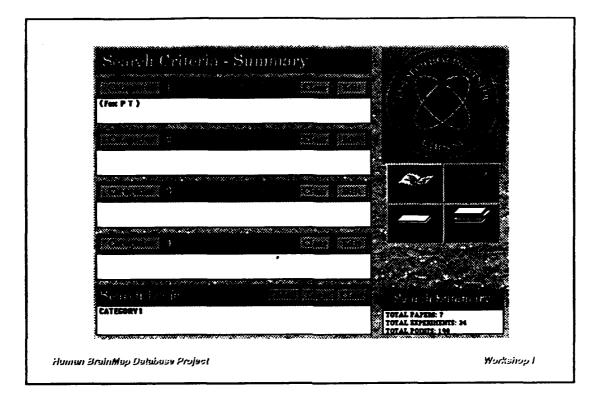Sean Marrett
Shawn Mikiten

APPENDIX F

BrainMap Users Guide

BrainMap Users Guide

The BrainMap user interface provides Search and View functions for the database. Search criteria are established and searches made from the Search Criteria - Summary screen. Results are viewed starting from the View - Summary screen. A brief outline of the capabilities of the BrainMap software follows:

BrainMap Users Guide

Searching begins at the Search Criteria Summary screen. There are four category boxes from which the user can select one each of the following:

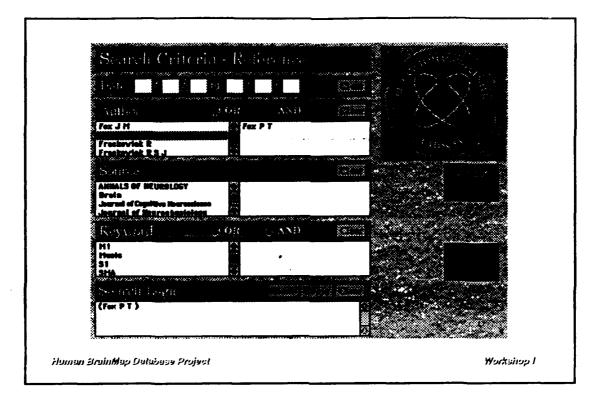1.   Reference
2.   Location
3.   Behavior
4.   Protocol

Category 1 must be specified before category 2 and likewise for the remaining categories.

Begin criteria selection by pressing and holding the Category 1 button. A pull-down menu will appear with the above four options. Selection of an option will bring up another screen with more detailed choices for that option (next four pages). On return the search logic selected will be displayed in the Category 1 box. Category 2 can now be selected in the same manner. The pull-down menu will now show that the option selected for Category 1 is no longer available. This process can be continued through Category 4 if desired. Each category can be cleared by pressing the Clear button with the category box. All selections can be cleared by pressing the Clear All button on.

Once the user has selected the desired Category or Categories, the search logic statements from each of the category boxes can be combined to form the final search logic. Pressing the Item button in the Search Logic box brings up a list of categories which have been selected. Select the categories and logic in the desired order. Each category item must be separated by a logical operator . Logical AND, OR, & NOT are selected using a pull-down menu accessed by pressing the Logic button.

When the search logic is complete press the Search button to begin the search. The Search Summary box gives the number of papers, experiments, and points found. Press the View Summary button to begin viewing the data. The Previous Set button can be used to return to the previous search criteria and data.
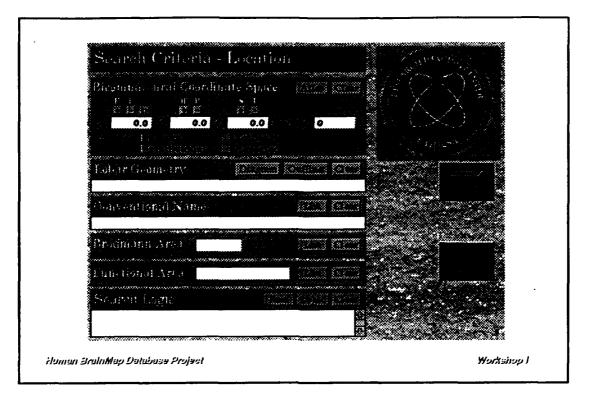
BrainMap Users Guide

The Search Criteria - Reference screen appears when Reference is selected as a category from the Search Criteria Summary screen. Four search criteria are available:

1. **Date:** Select a date criteria by typing a beginning and ending date. Date should be specified using the mm/dd/yy format.

2. **Author:** All authors within the database are listed in alphabetical order within a scrollable box. Select the author or authors by clicking on the name. AND & OR logical operators are provided for the author criteria.

3. **Source:** All journals within the database are listed in alphabetical order within a scrollable box. Select a single journal by clicking on the journal name.

4. **Keyword:** All keywords within the database are listed in alphabetical order within a scrollable box. Select one or more keywords by clicking on the word. AND & OR logical operators are provided.

Clear buttons are available for all boxes and the Clear All button will reset the entire Reference screen.

The Search Logic box is used to form the search logic statement from the four reference search criteria. Select the items and logic in the desired order. Each item must be separated by a logical operator . Logical AND, OR, & NOT are selected using a pull-down menu accessed by pressing the Logic button.

When the search logic for reference criteria is complete press the Back to Search Criteria button to return the Search Criteria Summary Screen.
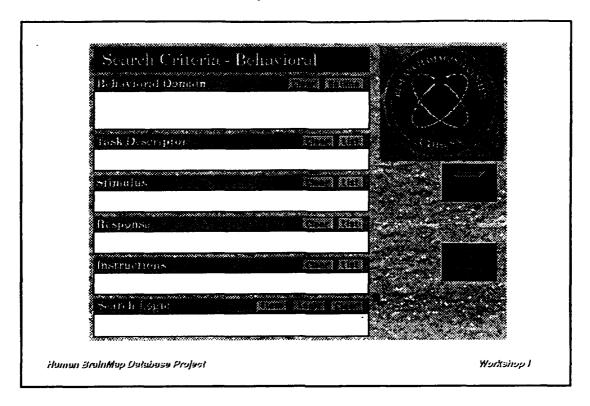
BrainMap Users Guide

The Search Criteria - Location screen appears when Location is selected as a category from the Search Criteria Summary screen. Five search criteria are available:

1. Bicommissural Coordinates: Coordinates can be selected by typing the appropriate x, y, & z values and a search radius. Additionally, the center coordinate can be selected graphically by pressing the Atlas button and selecting plot or a single section view. While working on the plot screen use the mouse to set the central point for the search. On return the x, y, & z values selected will be placed into the appropriate box. Points can be searched to include only mean, individual, estimated or reported coordinates by clicking on the appropriate check boxes. If none of the check boxes for this feature are selected the search will be based on location and radius only.

2. Lobar Geometry: Selection based on lobar geometry can be accessed either textually by pressing the Outline button or graphically by pressing the Diagram button. Select a single option and return.

3. Conventional Name: Press the List button for a list on conventional names. Select a single option and return.

4. Brodmann Area: Press the List button for a list of Brodmann's Areas. Select a single option and return.

5. Functional Area: Press the List button for a list of Functional Areas. Select a single option and return.

Clear buttons are available for all boxes and the Clear All button will reset the entire Location screen.

The Search Logic box is used to form the search logic statement from the location search criteria. Select the items and logic in the desired order. Each item must be separated by a logical operator . Logical AND, OR, & NOT are selected using a pull-down menu accessed by pressing the Logic button.

When the search logic for location criteria is complete press the Back to Search Criteria button to return the the Search Criteria Summary Screen.

BrainMap Users Guide

Search Criteria - Behavioral

Behavioral Domain

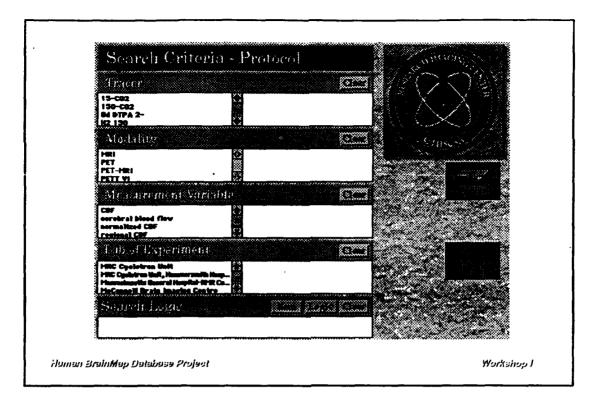Task Descriptor

Stimulus

Response

Instructions

Search Logic

The Search Criteria - Behavioral screen appears when Behavior is selected as a category from the Search Criteria Summary screen. Five search criteria are available:

1. **Behavioral Domain:** Press the <u>Outline</u> button to get an outline of the Behavioral Domain as specified for BrainMap. This is the same outline used when entering data into the database. Select an option by pointing and clicking, then return.

2. **Task Descriptor:** Press the <u>List</u> button for a list of Task Descriptors. This list is of data currently in the database. Select an option and return.

3. **Stimulus,** 4. **Response,** and 5. **Instructions** are selectable from lists as for Task Descriptor.

<u>Clear</u> buttons are available for all boxes and the <u>Clear All</u> button will reset the entire behavior screen.

The Search Logic box is used to form the search logic statement from the behavior search criteria. Select the items and logic in the desired order. Each item must be separated by a logical operator . Logical AND, OR, & NOT are selected using a pull-down menu accessed by pressing the <u>Logic</u> button.

When the search logic for behavioral criteria is complete press the <u>Back to Search Criteria</u> button to return the the Search Criteria Summary Screen.
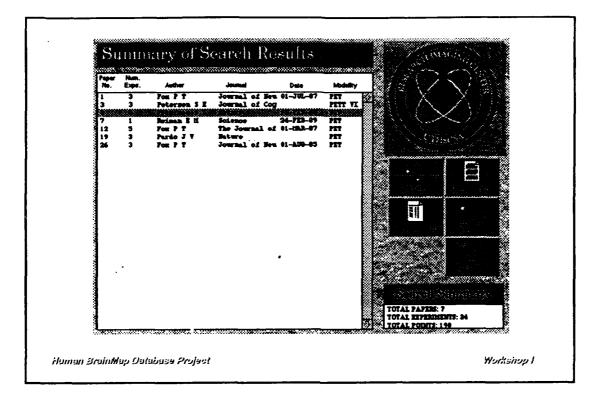
Fv

BrainMap Users Guide

The Search Criteria - Protocol screen appears when Protocol is selected as a category from the Search Criteria Summary screen. Four search criteria are available:

1. **Tracer:** All tracer data within the database are listed in alphabetical order within a scrollable box. Select a tracer by clicking on the name.

2. **Modality,** 3. **Measurement Variable,** and 4. **Lab of Experiment** criteria can be selected in a like manner.

Clear buttons are available for all boxes and the Clear All button will reset the entire Protocol screen.

The Search Logic box is used to form the search logic statement from the protocol search criteria. Select the items and logic in the desired order. Each item must be separated by a logical operator. Logical AND, OR, & NOT are selected using a pull-down menu accessed by pressing the Logic button.
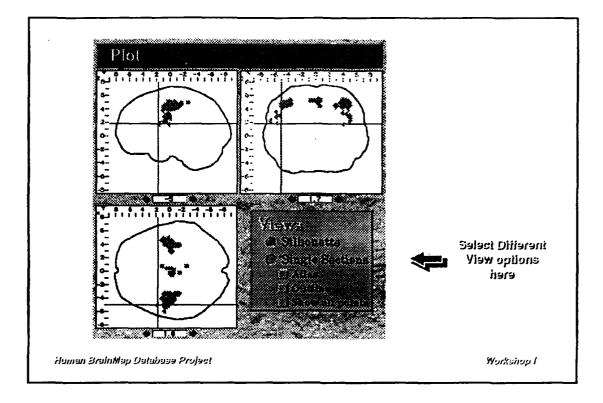
When the search logic for protocol criteria is complete press the Back to Search Criteria button to return the Search Criteria Summary Screen.

The Summary of Search Results screen lists the papers with experiments which match the search criteria selected used. The list includes paper number (internally designated), number of experiments for that paper, author, journal, date, and modality. Select a single paper by pointing and clicking for more information concerning reference, experiments, or locations for that paper. Multiple papers can be selected in the same fashion. Click again to remove a selected paper. Plotting can be used to compare the results when multiple papers are selected.

1. **Plot:** This is the most sophisticated route to begin the view process. A 3-view plot screen is accessed when the Plot button is pressed. On the 3-view screen all coordinates are plotted within silhouettes taken from three brains detailed in the Talairach Atlas (1967): axial (Hd6), coronal (vf25), & sagittal(s39g). Single viewing of coordinates with more detail is assessed from the 3-view screen (SEE NEXT PAGES).

2. **Reference:** The reference button should be used with only one paper selected. When pressed the Reference screen appears with option buttons to switch to Figures, Tables, or the Abstract screens. For papers with more than one experiment details for each of these screens can be accessed using the next or previous experiment arrow buttons.

3. **Experiment:** The experiment button should be used with only one paper selected. When pressed the Behavioral screen appears with option buttons to switch to population or protocol screens. For papers with more than one experiment, details for each of these screens can be accessed using the next or previous experiment arrow buttons.

4. **Location:** The location button should be used with only one paper selected. When pressed the Location screen appears with information dealing with coordinates on a point-by-point basis keyed to each experiment. For papers with more than one experiment, details for each of these screens can be accessed using the next or previous experiment arrow buttons.

All view screens are accessible from the plot screens. To make another search, return to the Search Criteria - Summary screen.
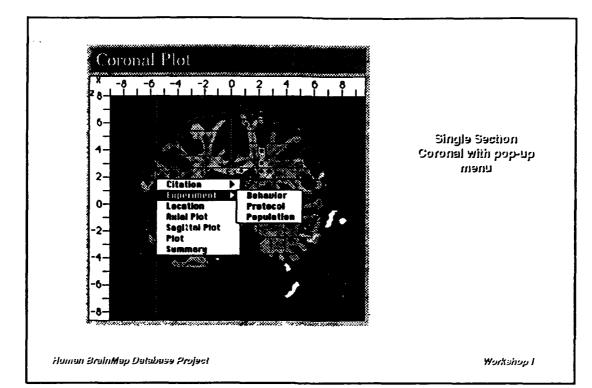
Select Different View options here

The 3-view plot screen appears when Plot is selected from the View Summary screen. Coordinates for all papers currently selected will be plotted by default. Each paper will be plotted with a different color and each experiment with a different numeric symbol. View options can be changed to single sections with atlas images or cortical grey matter outlines or both.

A suggested approach is to preview the 3-view plot data to visually determine the site or clustering of interest. Then point and click to bring the crosshairs to intersect at that site. The crosshairs are intended to help select the sectional view(s) which can be examined in greater detail. When the crosshairs have been positioned as desired, select a single section view using either the Axial, Coronal, or Sagittal buttons.

NOTES:

1. The 3-view plot for the Coronal view is from behind the brain, the Sagittal view from the left side of the brain, and the axial view is from above.

2. Crosshairs and view windows are color coded: axial-blue, coronal-green, & sagittal-red.

3. Color-to-Paper Assignment:

Coronal Plot

Single Section
Coronal with pop-up
menu

Citation
Experiment   Behavior
Location   Protocol
Axial Plot   Population
Sagittal Plot
Plot
Summary

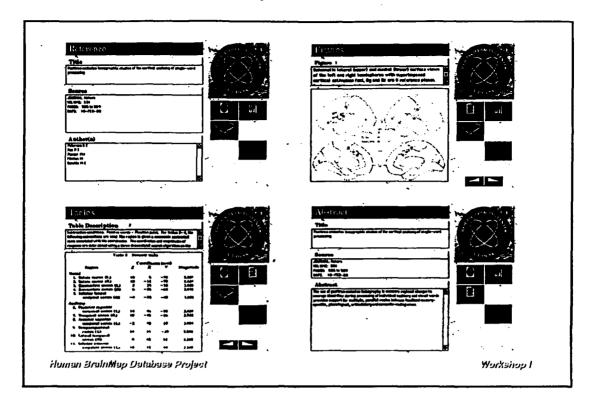Human BrainMap Database Project   Workshop I

The single-view plot mode offers the highest resolution for viewing coordinate data and greatest detail for accessing associated textual and numeric information. A pop-up menu is accessed by pointing at a numeric symbol and holding the mouse button down. This pop-up menu provides access to all data associated with the related experiment . A selection is made by moving the mouse (while the button is down) to highlight a menu item. The highlighted item is selected when the button is released. If no selection is desired, move the mouse pointer off the menu before releasing. After viewing the data from the selected screen, press the return to Coronal/Sagittal/ Axial button to return to the single-view plot.
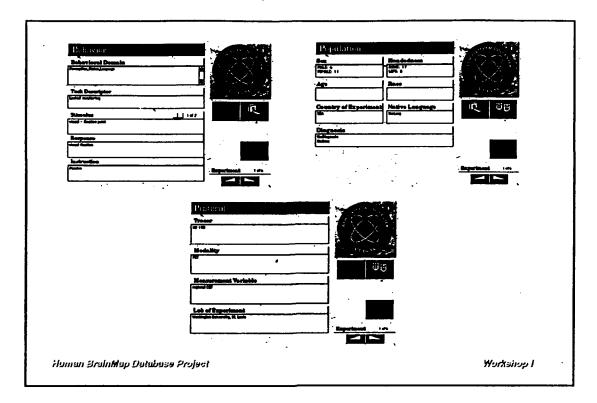
A small icon view showing the section location within an outline of the brain is provided. The section location is indicated by a line through the outline. Arrows are provided to change to adjacent sections. Additionally, sections can be accessed by pointing and clicking within the outline. The coordinate associated with the Talairach Atlas section is shown. The detailed single section view will be updated accordingly.

Coordinates within the section are indicated and updated whenever the crosshair is moved.

BrainMap Users Guide

The Reference, Figures, Tables, and Abstract screens provide buttons to move between each screen or to return to the View Summary screen. Additionally, if any of these screens are accessed via the pop-up menu in a single-section view, the Back to Summary button will indicate the appropriate plot view.
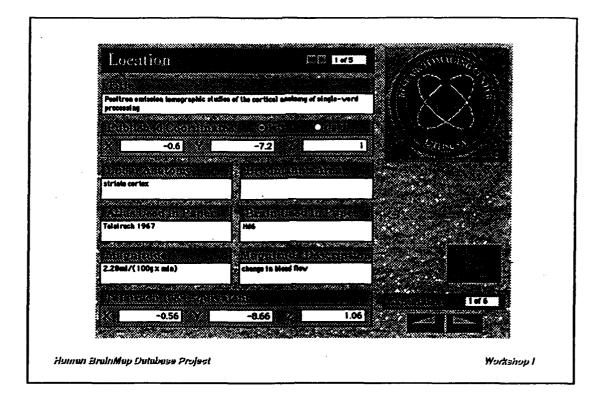
Figures and Tables are keyed to paper. Direction arrows are provided to view different figures or tables.

BrainMap Users Guide

When the <u>Reference</u> button is pressed on the View Summary screen the Behavior screen appears. The Behavior, Population, and Protocol screens provide buttons to move between each screen or to return to the View Summary screen. Additionally, if any of these screens are accessed via the plot pop-up menu the <u>Back to Summary</u> button will indicate to appropriate plot view.

These screens contain data at the experiment level. The experiment number can be changed using the arrow buttons. If these screens are accessed from a single-view plot pop-up menu, the experiment indicated will correspond to the numeric symbol selected.

The Location screen provides detailed information about each point in each experiment. Direction arrow buttons are provided to change point number or experiment number. If this screen is accessed from a single-view plot pop-up menu the experiment indicated will correspond to the symbol selected.

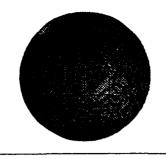Both published and Talairach 1988 equivalent coordinates are given for each point. Additional information concerning how the coordinates were determined is available.

APPENDIX G

Workshop Follow-Up Memo

Medical School
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Office of the Director

(512) 567-8100
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MEMORANDUM

Date: December 14, 1992

To: The BrainMap Advisory Group and All Participants of the Human BrainMap Database: Workshop I

From: Peter Fox and Jack Lancaster

Re: FOLLOW-UP PLANNING

Please accept our thanks for your participation in Workshop I. I believe all will agree that the Workshop was a great success. Enthusiasm for the concept of the database was embraced and the willingness of all parties to contribute to its evolution was gratifying. The Human BrainMap Database Project is officially launched.

Workshop II is scheduled for Saturday, December 4th - Monday, December 6th, 1993. This will give people a little breather after Thanksgiving.

We are working hard to transform the many excellent suggestions made during the conference into concrete design plans and a development schedule. Revised versions of the Users Interface and the Entry Interface will be released as soon as possible (early spring). The Entry Interface will include a facility for author entry and electronic submission of new papers. All papers will be checked before being incorporated into the Central Version of the shared database and redistributed. The goal of having the entire published literature in the database by Workshop II is realistic, with your help.

We are exploring the logistics of a BrainMap Bulletin Board.

A list of the working committees (interest groups) is appended together with e-mail addresses. We suggest that committees not wait for a bulletin board, but begin interactions by e-mail. We anticipate that a major component of Workshop II will be reports and recommendations form the working committees.

We will be resubmitting our proposal to the NSF for support of BrainMap development as quickly as possible. Letters of endorsement will be invaluable in demonstrating community interest and involvement. Several attendees have already sent strong, enthusiastic letters. If you want this project to move forward, write it down and send it in!

Again, our thanks for your involvement and encouragement.

APPENDIX H

Post-Workshop "Testimonial" Letters

George Carman	Hi
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Harriet Friedman	Hviii
Karl Friston	Hix
Patricia Goldman-Rakic	Hviii
Balázs Gulyás	Hx
Brian MacWhinney	Hxi
Bernard Mazoyer	Hxii
M-Marsel Mesulam	Hiv
Steven Petersen	Hxiii
Michael Posner	Hxiv
James Prichard	Hxv
Per Roland	Hxvi
Jerry Russell	Hxiv
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Robert Thatcher	Hxxiii
Don Tucker	Hxiv
David Van Essen	Hxxv
Chris Wood	Hxxvi

THE SALK INSTITUTE

January 12, 1993

Peter T. Fox, M.D.
Professor and Director, Research Imaging Center
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, Texas 78284-6240

Dear Dr. Fox:

I am writing to express my enthusiasm for the Human BrainMap Database, as described during Workshop I in San Antonio last month. As demonstrated to us during the Workshop, BrainMap is an extremely promising combination of software and hardware for the storage, retrieval, and analysis of functional imaging data. There are several attributes of BrainMap which provide key advantages over other potential tools for this purpose.

* Multimodal user interface (graphics, menus, and dialogue) for ease of use
* Universally accessible and computationally powerful hardware platform
* Multiple strategies for retrieval of data by author, paradigm, and anatomical locus
* Multiple representations of anatomy (coronal, parasaggital, and axial sections)
* Standardization of anatomical coordinates in the Talairach space
* Entry and exit points ("hooks") for local development of analysis tools
* Ability to enter data locally for comparison and analysis in context of the database
* Ability to maintain and distribute the database using Ethernet or other media

It is extremely encouraging to see that, after so much talk about the urgent need for such a database, that you have taken the initiative to actually get the job done. Your decision to involve a broad cross-section of the Neuroscience and Neuroimaging communities in the evaluation of BrainMap provides the means for the users to shape the tools early in their development. The ability to test and evaluate a beta release of BrainMap will provide these varied researchers with common experience with the tool, and provides an important avenue for constructive development in the months to come. at the next Workshop. I was impressed at the breadth and quality of representation at the Workshop in San Antonio, and am confident that these Workshops will provide an effective forum for resolving issues and questions as they occur.

Hi

I have installed the beta release of BrainMap on a Macintosh IIfx within our Central Biocomputing Facility at the Salk Institute. This facility serves as the bioimaging resource for a number of researchers at the Salk Institute, as well as our colleagues at nearby University of California at San Diego and Scripps Institute. By making BrainMap available for use and evaluation by the wider bioimaging community in San Diego, I hope to increase the efficiency of beta testing. I have established a simple mechanism for such users to report problems and log suggestions, which I will forward to you periodically.

Sincerely,

George J. Carman, Ph.D.
Salk Institute Vision Center

THE UNIVERSITY OF NEW SOUTH WALES

18 January, 1992

JAMES COLEBATCH, PhD FRACP
CONSULTANT NEUROLOGIST
AND SENIOR LECTURER

Dr. P. Fox,
Director,
Research Imaging Center,
The University of Texas Health Science Center,
7703 Floyd Curl Drive,
San Antonio, Texas 78284-6240
USA

Dear Peter,

   Thank you for inviting me to participate in the recent Human BrainMap Database conference. Functional 'activation' imaging in humans is a rapidly growing area which is already having an important impact on visual, motor and cognitive physiology. It is a field to which both PET and MRI (and perhaps other) imaging techniques are applicable and the results are of interest to a wide range of medical and non-medical scientists. It is the only method by which many hypotheses can be tested in the conscious human.

   The results of activation studies are likely to appear in a broad range of journals, reflecting the different backgrounds of the investigators. Apparently 'minor' results to one group may be crucial to another.

   A data base such as BrainMap can be a great assistance in this field. I particularly like the way that anatomically-based searches can be easily performed as well as searches on different protocols; searches which cannot be done with existing information services. It will also make different groups of workers aware of each others' work. Finally, from a purely Australian point of view, I particularly welcome initiatives which make us feel a part of the broader scientific community. BrainMap does this by providing information immediately via email, rather than us having to rely upon the printed journal, which usually takes 2-3 months to arrive here. At best, BrainMap could inform my colleagues and I of results of other workers well in advance of what otherwise would be the case.

Yours sincerely,

James Colebatch

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    512

December 15, 1992

Dear Peter,

re. BrainMap Database Initiative: Evaluation

Firstly, thank you for the opportunity to be involved in this worthwhile project. The concept is both innovative and timely. Since neuroimaging is inherently based upon anatomical constructs, the current text-based information systems for retrieval of prior and reporting of new research findings have major limitations. Your implementation of a knowledge base with a core anatomically driven search tool is both theoretically and heuristically sound. Your project should provide a seminal tool for anatomically based hypothesis generation, initially by PET workers but probably becoming a model for other imaging modalities. In addition, such laboratories should be able to enter their own preliminary data locally and collaborate with other laboratories using this tool as a standard display system.

There were some specific implementation suggestions. Creation of a 3-dimensional interactively rotatable coordinate system brain model, containing an averaged representation of the brain (such as the "average normal brain" of the Montreal Neurological Institute). This would be able to both accept user drawn areas of interest (ROIs) for coordinate-based searches and plot the coordinates of successful criterion-based database matches (eg using numbers as in the current implementation). The anatomical location could also be displayed in orthogonal planes (preferably not just standard x, y, z planes only) with or without the anatomical detail afforded by the Talaraich atlas or an equivalent. The database information which is mainly text-based could be specified by a dialog box, and then displayed interactively either upon clicking on individual database points or in a log window (allowing later printing and saving). A multiple window format would be desirable. Specific hooks allowing other local applications to both add and retrieve data are desirable.

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The workshop itself was also stimulating and helpful. It allowed focussed discussion of many of the abstract issues of methodology, standardization, imaging potential, terminology and computerization to be raised and evaluated. This process certainly facilitated our understanding of both the short and long term implications of this promising tool.

We look forward to ongoing testing and improvements in this highly worthwhile initiative over the next year, and hope we can contribute to its evolution and widespread dissemination.

Yours sincerely,

David Darby M.D. Ph.D.
Behavioral Neurology Fellow
Behavioral Neurology Unit
Beth Israel Hospital
Harvard University

M.-Marsel Mesulam, MD, PhD
Director
Behavioral Neurology Unit
Beth Israel Hospital
Harvard University

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neurologiques de Montréal

Institut d'enseignement et de recherche
de l'Université McGill

Montreal Neurological
Institute and Hospital

A Teaching and Research Institute
of McGill University

January 28, 1993

Dr. Peter Fox,
Director, Research Imaging Center,
University of Texas Health Science Center,
7703 Floyd Curl Drive,
SAN ANTONIO,
Texas, TX 78284-6240

Dear Peter and Jack,

I am pleased to lend my support to your efforts to establish a database of published results from the brain mapping literature. In our own laboratory we are constantly faced with the problem of extracting useful cross-validation information from other experiments, both from other labs and from other local investigators. To this end we have developed numerous tools for 3-D display/analysis of activation foci from more than one dataset. However, our procedures for parsing the available data for relevant datasets according to various search criteria are limited. Hence, your database addresses an immediate need for our group and, I suspect, any other group which has put a major effort into this area. The rapid growth of brain mapping with first PET and now increasingly with MRI and MEG/EEG plus the almost universal adoption of Talairach space as a common reference frame for reporting focal coordinates for activated regions provide compelling arguments for such a tool. Your initiative is not only timely but has a high likelihood of success given the existing framework for presenting results.

As was pointed out at the first workshop by many participants, while the conceptual goals are highly desirable and the first Macintosh-based implementation very helpful in demonstrating the potential of such a database, a more open design with hooks to Unix-based tools would be of great benefit to us. We definitely want to integrate the package into our global software environment. I hope we can be of some help in this regard.

We have recently instituted a series of workshops where the express purpose is to pull together results from experiments which may have had diverging primary goals but which together shed light on the role of specific regions. It is apparent that the BrainMap Database will be extremely useful in this exercise. I look forward to our continued

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collaboration and exciting times ahead in brain mapping.

Yours sincerely,

Alan Evans Ph.D.
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2

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January 26, 1993

Peter T. Fox, M.D.
Professor and Director
Research Imaging Center
The University of Texas Health Science Center
7703 Floyd Curl Drive
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Dear Peter,

We are writing in support of your proposal for support of the Brain Map project that you are submitting to the National Science Foundation. At the workshop, we were impressed with the progress made by your group in getting a database up and running and we think it will prove highly useful for the comparative analysis of PET studies.

Best of luck with your proposal.

Sincerely,

Patricia S. Goldman-Rakic, Ph.D.
Professor of Neuroscience

Harriet R. Friedman, Ph.D.
Associate Research Scientist

mmp

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of the Neurosciences Research Program
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Peter Fox MD
Research Imaging Center
The University of Texas.

Dear Dr Fox,

Human BrainMap Project

I am writing to thank you and the organizers for a full and enjoyable meeting and to provide you with some formal feedback. The conception and aims of the BrainMap project were, I thought, endorsed by almost everyone both on and off the floor. The questions people were addressing had passed beyond "do we need such an initiative" to "how can the potential of BrainMap be optimized". Indeed most people were more worried about how they could integrate BrainMap into their exiting analytical tools than whether they wanted BrainMap or not. I think there was consensus regarding the aims of the project, which seemed to be:

i) Defining standards for the communication of functional mapping studies.
ii) Providing a flexible and unique repository for data linked over several dimensions (topographical, behavioral, functional and methodological).
iii) The facilitation of hypothesis generation and meta-analysis.

In terms of scope it was generally accepted that the organization of the Database was appropriately restricted to: i) Voxel based analysis of neurophysiological data pertaining to human subjects, and ii) Data reduction to points in the standard stereotactic space. Despite the abundance of inspired ideas for future extensions, both in terms of data representation and stereotactic transformations, it was agreed to first phase would be a perfection of BrainMap within the context of these constraints.

With respect to "standards" the distinction between *standards to which one had to conform* and a *set of measurement standards* (eg which units to use) as a framework for comparison was established. The perception of standards as devices of constraint will be avoided if this distinction continues to be addressed.

Several key areas where targeted both for (i) consolidation and embellishment and (ii) future versions of BrainMap. In this regard I am delighted to participate in a committee focussing on the statistical issues that BrainMap raises.

Yours sincerely,

Karl J Friston MB BS MA(Cantab.) MRCPsych

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Dr. Peter T. FOX
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6 December 1992

Dear Peter,

Ref.: Human BrainMap Workshop, 29 Nov - 2 Dec, San Antonio

Many thanks for the invitation and all the arrangements you have made
for me. It was a pleasure to participate in the workshop. Congratulations to
you for the fine organization and the very high level workshop.

We keep in touch. I am looking forward to seeing you again in San
Antonio.

With my very best wishes,

Yours sincerely,

Balázs Gulyás

Hx

Carnegie Mellon

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Friday, January 15, 1993

Dr. Peter Fox
Research Imaging Center
Biomedical Image Analysis Division
University of Texas Health Sciences
7703 Floyd Curl Drive
San Antonio, TX

Dear Dr. Fox:

It was good to hear that you are planning on following through with the various BrainMap initiatives that were sketched out during the Advisory Group planning meeting in San Antonio at the beginning of December. The importance of this work and the enthusiasm it is generating within the neural sciences community is quite impressive. As I currently see it, the Brain Map project has the potential of becoming the central information organizer for research in brain functioning, so that new research projects are not even initiated without making use of the database of accumlated knowledge about functional mapping that will be available through the BrainMap system.

I very much appreciated the opportunity to share the experiences learned by the child language community in the establishment of the CHILDES database with your people. I believe that we both benefitted a great deal from the interchange. There are many difficult issues of copyright and ownership that are less serious problems for your project than they were for our project. However, both projects confront very similar technical issues in terms of network communications, database updating, and software development. I will be happy to continue to work with you and your programmers in these areas.

I also hope to provide input regarding some of the ways in which the theory of cognitive psychology and information-processing more generally can help inform the information retrieval system and the way in which data is encoded in the database. In this area and in the others I have mentioned, your project has my full support.

Yours truly,

Brian MacWhinney
Professor of Psychology

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

ROBERT DEBRÉ

Paris, January 8, 1993

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Réf. BMM/YG/93/003

Pr P.T. Fox
Research Imaging Center
Health Science Center
University of Texas at San Antonio

Dear Peter,

Workshop I of the Human BrainMap Database project held in San Antonio last December has been a clear demonstration both of the importance of a concerted action in the field of Brain Mapping and of the enthusiasm of the participants. As a member of the Statistical Descriptors and Standards group of this initiative, you can certainly count on my active participation to this project.

With my best regards.

Bernard M. MAZOYER, Ph.D., M.D.
Professor of Biostatistics and Computer Science
Head Neurofunctional Imaging Group
Xavier Bichat School of Medicine, Paris and
Service Hospitalier Frédéric Joliot, Atomic Energy Commission

TO: Peter Fox

FROM: Steve Petersen

RE: BrainMap Project

This letter addresses issues related to the BrainMap Project, the associated meeting, issues related to organization, and the special working groups.

Meeting: I think that for an organizational meeting of this type, it was quite productive. There was significant information passed, and the issues that needed to be discussed were given a fair airing. The organization and efficiency of the meeting deserve high praise. Some suggestions for the future: If the meeting is to be opened to a larger community, then perhaps the meeting should be made into parts with the advisory board meeting slightly before or after (or 1/2 day before and after) the more open parts of the meeting. After the next general meeting, it will be likely that more specials small meetings, or consults from individuals will be more useful.

Database: From the demonstrations and hands-on experience at the meeting, the database looks like a potentially valuable addition to the area of functional imaging. Again the first approximation organization seems well-conceived to act as a good reference source, and for the generation and "meta-testing" of hypotheses for the generation of future experiments. While there will certainly be bugs discovered, the general approach seems to strike a good balance between openness and focus. The openness will be useful in allowing interfaces to other programs, and the focus allow problems to be addressed in a reasonable time frame. Clear issues from the meeting include the need to remain open to discussions of other spaces (stereotactic or unfolded, etc.), as well as more complete descriptions of responses. Its utility for PET and functional MRI is clear at this point, but the interfacing with data from EEG and MEG will take significant creativity and work.

Working groups: I am less sanguine about the working groups concept. Unless the leaders of these groups invest a lot of effort, there will probably be little gained from them. Since the leaders, in general, have no vested interest (other than scientific altruism), the group effort will probably be expended in the week preceding the meeting next year, unless significant prodding is done by you. Also, I think that I should be included in the behavior working group.

All in all, I think that you have made and excellent and admirable beginning to a very tough project.

Sincerely

Steve Petersen, Ph. D.
Assoc. Prof.

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UNIVERSITY OF OREGON

11 January 1993

Peter Fox, M. D.
Research Imaging Center
University of Texas Health Sciences Center at San Antonio
7703 Floyd Curl Drive
San Antonio, TX 78284-7801

Dear Peter:

We have installed BrainMap in our laboratory and we are very excited about it. We think this is an important resource for the scientific community.

As you know, our perspectiveis that of a brain electrophysiology laboratory. We therefore have different forms of data than PET labs, with differing demands for graphics and database management. However, the common anatomical frame provided by BrainMap, withthe bicommisural coordinates, provides a reference for registering various forms of brain activity.

An example of the research that BrainMap has inspired is the Head Conductance Atlas, our project to characterize the conductance values of head tissues of average dimensions to facilitate analytical solutions of the inverse problem for localizing sources of brain electrical activity recorded at the scalp.

We feel BrainMap is a pathfinding project, and will be very important toresearchers studying electrical and magnetic data in an anatomical framework. Good luck in your efforts to obtain funding.

Sincerely,

Don M. Tucker, Ph.D.
Professor of Psychology

Michael I. Posner, Ph.D.
Professor of Psychology

Gerald S. Russell, MSEE
Graduate Teaching Fellow

Hxiv

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Mon 7 Dec 92

Dr Peter Fox
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Dear Peter:

I very much enjoyed the workshop, and I learned a great deal. What was discussed is but the beginning of a very big subject. The implications go far into the neurobiology and clinical practice of the next century.

Much that was said at the meeting was new to me, apparently including some of your own studies. I would be grateful for reprints of your recent and what you consider your most important work.

Besides learning things I don't know, I wish to make slides for use in two series of lectures that I will give next year during visiting appointments at The Royal College of Surgeons in London and the Ecole Polytechnique south of Paris. My practice when using the work of others in lectures is to include a slide of the title page. The audiences will be mostly NMR spectroscopists who want to hear about modern neuroscience research in vivo. I have a collection of PET and MRI material to go with the MRS that I know best, but much less on current PET studies mentioned at the meeting. Word on those things from papers selected by the author would benefit both my audiences and myself.

Sincerely,

Hxv

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Professor Peter Fox, M.D.
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1993-01-21

Dear Peter Fox,

As a member of the BrainMap advisory group, I was pleased to
participate in the first workshop. The BrainMap initiative, and the
workshop came very timely. It meets an urgent need for a forum of
communication between scientists involved in physiological and
biochemical recordings of the human brain. In non-human primate
physiology and neurobiology, the detailed macroscopical structure of the
monkey brain, and cytoarchitectural regions have usually been used as a
frame of reference. However the variations in brain anatomy and cyto-
architechtural fields within the same species have never been
addressed, although it is considerable. In the human brain the variability
is much larger. Consequently it is of great importance now for the first
time to establish an anatomical frame of reference, which can be used by
all primate neuroscientists working with human brains and subsequently
also monkey brains. The use of this increases the scientific value of the
single publications and the BrainMap in its present format is a good
start.

We have here installed the BrainMap database and are making it
available for all workers in human functional mapping in Scandinavia.

It is important that this initiative becomes more formalized. That is,
future workshops should be arranged and the BrainMap database should
be enlarged and new databases perhaps in the form of average magnetic
resonance tomograms of normal subjects should preferably be added to
the database to replace the present single brain used by Talairach and
collaborators in 1988. Single laboratories are often using advanced
anatomical standardization schemes which could be attached to the
BrainMap.

Within the field there is also a great demand for more specific behavioural categorization of the different tasks, a need for development of an anatomical nomenclature and needs for further development of statistical descriptors of brain activation. These discussions most naturally take place within the BrainMap community. It is therefore my hope that the initiative that you and your collaborators have taken thrive and grow rapidly.

Yours,

Per E Roland

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January 27, 1993

Peter T. Fox, M.D.
Professor and Director
Research Imaging Center
The University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, TX   78284-6240

Dear Peter:

Thank you for inviting me to serve on the Advisory Board for your Human BrainMap Database project. I enjoyed attending your first workshop in San Antonio and am looking forward to further stimulation at the subsequent meetings.

As per your request, this letter contains brief comments with my evaluation of the status and plans for your project. Hopefully, this will help you to gain funding for future workshops and for continued development of the database.

You have rightly focused on the problems of a small and well-defined community, which is nonetheless of great importance to the neuroscience community at large.   Your users and advisors include an excellent and influential set of the research investigators who study functional imaging with PET (and MRI) scanners. In addition, you are already reaching out to the communities for major non-invasive technologies for human functional mapping such EEG/MEG and ERP. This is clearly reaching an appropriate set of people to effectively evolve and use such a brain mapping database.

With regards to the database generation itself, you are addressing most of the major issues well and the workshop set up an appropriate set of working groups to further address these. To support the database as a sharing medium, it is essential to have both a standard metric for representing the data and standard classification for categorizing the data. For the former, the Talairach atlas seems adequate to serve as a standard metric, although it

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eventually need to be replaced by something better, such as an averaged brain, as discussed at the workshop. For the latter, your laboratory has made a significant start towards classification for functional behavior and the working group is sure to evolve this further. So metrics and classification seem in good shape.

With regards to the contents of the database, you have made a good start by having your laboratory enter the data directly contained in the core literature. It was clear from the discussions at the workshop, and has also been my experience with molecular biologists, that there will rapidly be demand for the complete set of checked data. That is, first quality data part of the same experiment but not actually published in the papers, then "raw" data from other experiments which have not yet been published. To get the literature in as soon as possible, I would urge you to implement a direct submission procedure in addition to working with key labs to get their own local databases into your standard format and central archive. (And also require database submission as a prerequisite for publication in journals edited by you and your advisory board.) It is good that you are making the connection with the GenBank project, who have gone through similar stages with DNA sequences. For submitting and especially quality checking more raw data, you will probably need extensive electronic support. It is probably best, just as you are doing, to concentrate on the formal literature first and wait for greater maturity of software systems for handling community knowledge within an integrated environment, such as the one I am working on in molecular biology.

With regards to the software, the current system based on the commercial technology of Supercard and Oracle is not adequate for many purposes. As we discussed, you will likely get some speed improvements by moving to a separate back end server on a UNIX workstation, but will eventually run into the hard limits of the software technology, especially of relational databases, just as GenBank and the Genome Database (human gene data) have. This will be a particular problem when you wish to begin to incorporate analysis programs to build a complete environment for analyzing research data, rather than simply retrieving exactly specified images. By that time, you will need to look hard at the state of research-quality database software. A problem you will encounter earlier centers around your choice of hardware platform. An Apple Macintosh seems too underpowered for the demands of real-time interaction with 3D brain models and browsing functional images.

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The best available analysis programs tend to run on graphics workstations, such as a Silicon Graphics IRIS, and I would be tempted to say that any lab which can afford a PET machine can afford a graphics workstation for critical analysis.   I would recommend you survey your user community more carefully on this issue.

In conclusion, you have made an excellent start towards generating a brain mapping database for human functional images. Your scaling is good and you have laid all the . appropriate groundwork for implementing an effective and quality database and process. Your software developments have been less successful and you are rightly concentrating on the database development itself. I would be personally quite interested in collaborating with you to insure that the software provides the same level of quality service to the community as your database, particularly as a test case in neuroscience of my community system technology currently under development in molecular biology. Your success in building the foundational database will help us all. Thus I wish you the best of luck in gathering the necessary resources.

Sincerely,

Bruce R. Schatz

Bruce R. Schatz, Ph.D.
Director, Community Systems Laboratory
University of Arizona

Hxx

1

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Peter T. Fox, M. D.   December 17th, 1992
Professor and Director
Research Imaging Center
The University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, Texas

Re.: Workshop I, Human Bain Map, San Antonio, November 29th - December 3rd, 1992.

The workshop was directed at presenting a digitized medium for meta-analysis of PET activation studies on the human brain. As was pointed out at the meeting the results of the different PET-groups are difficult to remember in detail and therefore to relate to each other. There is no doubt that a database is needed to provide an objective tool to map the activation fields reported by the different research groups for the different stimulation tasks. A prerequisite for the project is that requirements of statistics are fulfilled in the data and that the areas of activation are communicated in the stereotaxic space of Talairach. While most PET centers adhere to this regimen, single case studies and functional MR imaging will also be included, if they conform with these rules. Much time was spent on the refinement of the user interface with respect to speed limits due to an increasing amount of data, specification of technical and experimental details, search strategies, data display, and exportation of results. Finally, the most important goals for the coming months were prioritized in an open panel discussion.

Altogether, it was an extremely well organized and very stimulating meeting. It lived from the intensive discussions of outstanding experts on a well guided list of critical issues fundamental to the set-up of the entire project.

Hxxi

December 5, 1992

Dr. Peter T. Fox
Research Imaging Center
UTHSCSA
7703 Floyd Curl Drive
San Antonio, TX 78284-6240
U.S.A.

Dear Peter

Congratulations again on such a well organized and successful workshop. I must admit that I am quite impressed by the progress you and your colleagues have already made. I am convinced that **Brain Map** will be a useful and powerful tool for reference and research. The choice of ACM is very well balanced and you are to be commended on that. I am really pleased to be part of this enterprise.

We attempted to install the program last night and we should have it today. I will keep you posted.

I am sorry that I had to leave early on Wednesday, as I had mentioned to you. I was expected to be in Quebec City for a grant review committee that same day in the afternoon, and I just made it.

Thank you again for this great initiative.

Yours sincerely

Justine

Justine Sergent

IIxxii

DEPARTMENT OF HEALTH & HUMAN SERVICES   Public Health Service

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December 10, 1992

Peter T. Fox, M.D.
Research Imaging Center
UTHSCSA
7703 Floyd Curl Drive
San Antonio, Texas 78284-6240

Dear Dr. Fox;

I want to thank you for inviting me to "The Human BrainMap Database: Workshop I". It was very well organized and I believe a lot of progress was made toward improving and further implementing the data base. The following are thoughts and comments regarding some of the issues raised at the Workshop.

1- This is a unique endeavor that is badly needed in the burgeoning field of neuroimaging. Nothing like this data base currently exists in the field of neuroimaging. Its strengths include its ease of use and upgradability for the integration of anatomy, electrophysiology, functional imaging and behavior.

2- Considerable discussion was devoted to the use of "Bicommissural coordinates". It was generally agreed that, although there are limitations, BC coordinates are a good beginning. BC coordinates will provide a common reference frame or coordinate system so that a variety of studies can be spatially related. After an individual achieves an approximate organization of studies he or she is interested in, then more rigorous analyses can be conducted by the individual investigator themselves. The idea of eventually adding multiple cross-linked coordinate systems to the data base was generally accepted by all present. For example, Alan Evan's >200 subject MRI data base should be cross-linked to the BC at some point in the future.

3- Increased speed was a generally recognized need. However, the current system is adequate to get people to use the data base and once the "bugs" are identified and corrected then increased speed through a compiled version can be

implemented. Server networking also seemed to be a good idea for increasing speed where individual MacIntoshes can be connected to a central server system.

4- An important recommendation is the addition of a modeling section to the data base. This is especially important as studies of multimodal registration become more frequent. A growing number of mathematical models and simulations of PET activation and MRI activation are being published, thus there is already a strong need to add model as a category and so that correlational analyses and simulations can be evaluated.

5- The integration of EEG/MEG to the data base does not need to be delayed. For example, those studies involving registration of electrophysiological dipoles to MRI and PET are immediately translatible into BC coordinate space. Once a standard coordinate system is agreed upon, e.g., the Cantho-Meatal line, or the PPN system, then translation of all human scalp electrophysioligcal/MEG studies to the BC line can occur.

Once again thank you for putting on such an excellent workshop.
With warm regards.

Sincerely,

Robert W. Thatcher, Ph.D.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

AT WASHINGTON UNIVERSITY MEDICAL CENTER

David C. Van Essen, Ph.D.
Edison Professor of Neurobiology

Head, Department of
Anatomy & Neurobiology

January 27, 1993

Dr. Peter Fox
University of Texas Health Sci. Ctr.
Research Imaging Center
7703 Floyd Curl Drive
San Antonio, TX 78284

FAX: 210-567-8152

Dear Peter,

I am writing to let you know of my enthusiastic support of the efforts you have made in establishing BrainMap as an important new approach to accessing information about structure-function relationships in the human brain. The workshop that you held in November came at just the right time, as your software team had produced something sufficiently well developed that we could all put it through its paces, yet not so advanced that feedback would be arriving too late to be useful. Just as importantly, I was thoroughly impressed by the receptiveness that everyone on your team showed in response to the many constructive suggestions and comments that arose during the workshop.

As soon as I returned from the workshop, I gave a brief tutorial to members of my lab on how to use BrainMap. Postdocs and graduate students alike were intrigued by it and have in fact used BrainMap on multiple occasions to explore results from PET studies that are relevant to our own research on the primate visual system.

In my opinion, BrainMap has the appropriate scope to serve as an extremely valuable pilot project in bringing graphically oriented databases into common use in neuroscience. It tackles an important practical problem that is of widespread interest to a focussed, computer-literate community. From the discussions at the workshop as well as conversations I have had elsewhere, it is also clear that there is widespread respect and appreciation in the functional brain imaging community for your leadership in getting this effort successfully launched.

As you know, I am very interested in helping to establish an analagous type of graphically oriented database that would focus on the organization and connectivity of different cortical areas in the macaque monkey. It seems likely that the basic platform you have developed for the human brain may also be well suited for such efforts on nonhuman primates. I hope that we will have an opportunity to explore this possibility in the not too distant future.

Sincerely,

David C. Van Essen

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Date: January 25, 1993

Refer to: P-6:012593

Dr. Peter Fox, Director
Research Imaging Center
University of Texas
   Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-6240

Dear Peter:

I wish to indicate my enthusiastic support for the Human BrainMap Database project and my continued willingness to serve on the Advisory Committee. I believe that you have carved out an important and well-motivated niche in the multi-dimensional (and often conflicting and confusing) space of "brain database projects" discussed in the NAS document and followup NIMH/NSF discussions. On one hand, by focusing initially on published PET data you have identified a problem scope that is both useful and doable. On the other hand, your strategy of discussing the inclusion of other imaging modalities (e.g., functional MR, electromagnetic recordings, lesion deficit data, etc.), pre-publication as well as published data, and alternative spatial coordinate systems to the Talairach system *from the very beginning* ensures that the BrainMap project can evolve in a flexible and constructive way.

In planning future meetings of the Advisory Committee, I would recommend that you separate the following two functions (which were understandably combined in the initial Workshop) into different meetings: (1) a roll-up-your sleeves working meeting of the Advisory Committee, dealing with substantive critical evaluation of the project; and (2) a more public forum, open to all interested parties, to present the goals and accomplishments of the project. Of necessity, the initial Workshop included an overview of the project and introduction to associated software for the Advisory Committee, and it made sense to include other interested parties in those introductory sessions. However, it will be more efficient and productive to separate these two functions in future meetings.

I look forward to continued involvement in the BrainMap project. Best regards.

Sincerely,

Charles C. Wood
Group Leader

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APPPENDIX I

"Databasing the Brain," <u>Science</u> (1992) 5909: 1872-1873

Databasing the Brain

Neuroscientists aim toward a confederation of databases that would let researchers wander through the brain from molecules all the way up to function

At the top of the brain is a bundle of fibers that poses a long-standing challenge to neuroscientists. The challenge is quite basic: Nobody knows what the front third of this bundle, the cingulate gyrus, does. So, when Washington University neuroscientist Steven Petersen attended a workshop* on databases recently, the cingulate gyrus struck him as just the thing for putting a prototype neuroscience database through its paces.

Petersen sat down at the keyboard, punched in the structure's name, and, in short

Data template. BrainMap's screen display.

order, the database (dubbed BrainMap) coughed up five studies in which human subjects performed complex motor tasks while the activity in their anterior cingulates was monitored by positron emission tomography (PET). A few minutes later, the screen showed an outline of a human brain with a graphic summary of how the parts of the cingulate seem to be involved in motor tasks. Petersen, for one, was impressed: "If we had all the data in one place like this, maybe we could figure out what this mysterious area is doing."

That hope—that having all the data in one place will shake loose new insights about how the brain works—is driving a surge of interest in neuroscience databasing. Last year, the Institute of Medicine (IOM) enthusiastically endorsed what it called the "Human Brain Project," an ambitious, two-decade effort to develop a set of neuroscience data-

*"BrainMap Workshop I," 30 November to 2 December, at the University of Texas Health Science Center in San Antonio.

bases (*Science*, 28 June 1991, p. 1794). And when the National Institute of Mental Health (NIMH) held an all-day workshop on the project at the Society for Neuroscience meeting in Anaheim in October, 400 neuroscientists crowded in, and more were turned away at the door. Indeed, the vision of a neuroscience community linked by databases is already becoming a reality: Several progenitor databases, including BrainMap, are under development and will compete early next year for millions of dollars in federal funding set aside for pilot studies for the Human Brain Project.

In one sense, neuroscientists are simply following the lead of the geneticists, protein modelers, and molecular biologists who have already gone on line to share a single, relatively standardized kind of data with their colleagues. But California Institute of Technology neuroscientist Jim Bower, who has developed Genesis, a three-dimensional simulator of brain circuits, argues that "what neuroscientists are trying to do is orders of magnitude more complex." He and other database visionaries see BrainMap and its like ultimately growing into a network spanning the entire range of subfields in neuroscience, from studies of the brain's molecular and cellular workings, to brain mapping, and all the way up to cognitive psychology.

That, they say, would open the way to some powerful cross-fertilization. "Molecular biologists working on the brain don't read too much cognitive psychology," says Michael Huerta, a neuroscientist who is chief of the neural systems program at NIMH. "But the point of these networks is to allow the integration of this kind of information." Cognitive psychologists could tie their theories about the workings of the brain more closely to actual structure, while molecular biologists could begin to see how the structure in the neurons relates to overall function. Researchers might be able to pinpoint more precisely the underlying brain damage that causes Alzheimer's disease, schizophrenia, or stroke, while those who compare

animal brains with humans might find better animal models for studying disease or testing new drugs.

Standing in the way of that vision are some daunting technological and sociological challenges, as well as funding worries. But if brain science's effort at grand unification succeeds, it will provide a model for other fields, such as ecology, that also could profit by merging data from many different lines of investigation.

A PET project

The first hints of that kind of unification are already evident in efforts like BrainMap, which is slowly expanding from a single, specialized data catalogue into something more comprehensive. When it all started in the mid-1980s, says University of Texas neuroscientist Peter Fox (BrainMap's main developer along with University of Texas physicist Jack Lancaster), he was just trying to cope with his own PET data. Recalls Fox, then a researcher in brain imaging pioneer Marcus Raichle's lab at Washington University in St. Louis, "It became obvious to me I couldn't keep all the observations of my data in my head," says Fox. "So, I played around with ways to create a database to allow me to explore my data to see if a hypothesis about it was viable or not." Then he heard about the community databases in which geneticists were storing the sequences for genes as soon as they submitted them for publication. Fox realized how useful it would be if neuroscientists also could pool their data, and he convinced several foundations and government agencies to fund his efforts to design a database of brain mapping data.

The result is the "prototype" database that Fox tested on Petersen and three dozen other neuroscientists at the workshop in Texas earlier this month. In its current form, BrainMap contains the data from 30 published journal articles representing several hundred experiments, most of them involving PET data. After BrainMap goes on line with 150 articles—over the Internet in about 6 months—Fox hopes it will grow rapidly. And while BrainMap now comprises primarily PET scanning data, he hopes to expand it to contain images of the brain from other mapping methods, such as magnetic resonance imaging (MRI), magnetoencephalography (MEG), and electroencephalography (EEG), as well as studies of the effects of brain lesions.

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Harvard University neuroscientist Marsel Mesulam, for one, is looking forward to that broadening: "A criticism of brain lesion studies is that they only tell you what the brain does without the lesioned area, rather than telling you what the lesioned area does," he says. Comparing brain lesion studies with functional brain mapping—in which neuroscientists link motor, visual, and other functions to specific areas—should sharpen the overall picture of the brain. Neuroscientist David Van Essen of Washington University foresees even greater gains if the database is expanded to include PET scans of animal brains, some parts of which are known in far more detail than the human brain because studies can be more extensive. If the database makes it possible to transfer to humans the detailed picture he and other investigators have developed of the visual system in macaques, it could lead to a better understanding of human vision and, perhaps, new therapies for some visual disorders.

Elsewhere in neuroscience, other databases are springing up that may eventually join BrainMap in the larger network of databases. Using cutting-edge computing technology, Bower at Caltech is turning his computer simulations of brain circuits into a database to try to understand the functional organization of the nervous system. Meanwhile, Scripps Research Institute neuroscientists Floyd Bloom and Warren Young have developed an on-line atlas of the rat brain, known as the Brain Browser, and are trying to expand it. Scripps has hired three software programmers to develop the Browser into something more like an on-line encyclopedia for the community, which eventually should include images and data on the biochemistry and circuitry of the rat brain.

Learning to share

Even before they are linked in a set of community-wide databases, though, these efforts have encountered some of the hurdles that stand in the way of that larger confederation. As BrainMap expands to encompass other kinds of imaging data, for example, it is running into a problem Fox has managed to avoid so far—the need for consistent data standards. The neuroscientists who use PET had already taken care of that problem by setting an international standard for labeling parts of the brain with coordinates rather than names, making it possible to compare data obtained from different brains or by dif-

ferent techniques. But that kind of standardization doesn't come easy. "A lot of fields haven't gotten past this point of how to represent their data," says Bruce Schatz, an information specialist at the University of Arizona, and architect of the Worm Community System (WCS) database, which links researchers studying the nematode worm *Caenorhabditis elegans*.

Bower, in his brain circuit database, has been grappling with another issue that plagues all databases: quality control. "No one wants a database of junk," as he puts it succinctly. By junk, Bower means not just data entered incorrectly (he's got safeguards for those) but also data that are just plain uninteresting. "Just listing the 85 potassium channels is not particularly satisfying if you're interested in how the cell system works," he says. The key, says Schatz, is to establish a quality-control process within the system to make sure the entries are credible and useful.

Fox, meanwhile, has had an early taste of what is bound to be a controversy about what kind of data to archive—and how to control access to it. He'd like to see BrainMap come to include both published and "raw," unpublished data—or at least the complete data sets that were published in condensed form in journals. By giving researchers a more complete picture of their field than published data alone can offer, says Fox, "BrainMap should help labs cut duplication of experiments, and make them more efficient."

But the prospect of making raw data available to a wider community raises sticky questions, says Schatz. Databases will need mechanisms not found in commercial software to allow researchers to determine who will see the raw data—whether they limit access to their own lab or a few collaborators, or offer it to the entire neuroscience community. There's also the question of when raw data should be unveiled. Fox raises the possibility of an arrangement with journals publishing in the same field, in which scientists would be encouraged to archive their underlying data in the database when they publish, much as geneticists already do. Even if Fox, Bower, and other database
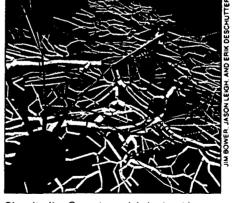

BrainMapper. Database designer Peter Fox and his creation.

pioneers get their databases up and running, the ultimate challenge will be merging them. Designers will have to build a single software environment to link lots of labs running separate programs and databases on all kinds of different computers. The object is to allow scientists—even those without special computer skills—to browse easily from database to database. What's needed, says Schatz, is "a system that lets you concentrate on navigating between different pieces of data rather than dealing with each individual database and program."

All this, of course, won't come fast or cheap. The final hurdle will be funding—and estimates of the ultimate cost range from tens of millions to billions of dollars. Beyond the first few million, expected to come early next year from the many federal agencies participating in the Human Brain Project, prospects are uncertain.

Other communities are intently watching neuroscientists' efforts to negotiate these hurdles. Says Dan Sulzbach, executive director of the San Diego Supercomputer Center, who is working with ecologists to build a community database that could include satellite images: "We're interested in how neuroscientists solve the problems of how to store the data, how to access it, and what kinds of queries you use to access images, for example." Ecologists, like archeologists and other researchers, recognize that they too could benefit by making data from many different subfields available at the same time to a single investigator—letting him or her see all parts of the elephant at once.

And there's another impetus for databasing that is certain to grow in the future, bringing more and more fields into the fold: "There will be masses and masses and masses of data," says Sulzbach. "There's going to be so much data that individual researchers won't have the facilities or personnel or interest to manage all that data"—whether it is images of the brain, Earth from space, or the genes in different organisms. Smart databases that

Circuit city. Genesis models brain wiring.

can scan this huge universe of data and focus on an object of interest are fast becoming critical tools for future scientists. And as a few scientists master those new tools and publish the resulting breakthroughs, it will only be a matter of time before their colleagues will want to go on line as well. Says Young at Scripps: "They'll have to move in this direction, or they'll be out of it."

—Ann Gibbons